UNITED STATES OF AMERICA

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

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DIVISION OF ONCOLOGY DRUG PRODUCTS

ONCOLOGIC DRUGS ADVISORY COMMITTEE

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54TH MEETING

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THURSDAY

SEPTEMBER 18, 1997

The meeting took place in Versaille s Ballrooms I and II, Holiday Inn Hotel - Bethesda, 812 0 Wisconsin Avenue, Bethesda, MD, at 1:00 p.m., Janice J. Dutcher, MD, Chairman, presiding.

PRESENT :

Janice J. Dutcher, MD, Chairman
Jannette O'Neill-Gonzalez, MHS, Executive Secretary
David H. Johnson, MD, Member
James Krook, MD, Member
Kim A. Margolin, MD, Member
Robert Ozols, MD, PhD, Member
Derek Raghavan, MD, PhD, Member
Richard L. Schilsky, MD, Member
Richard M. Simon DSc, Member
Sandra Swain, MD, Member

PATIENT REPRESENTATIVE PRESENT:

Kenneth Giddes

CONSUMER REPRESENTATIVE PRESENT:

Desmar Walkes, MD

FDA REPRESENTATIVES PRESENT:

Robert DeLap, MD, PhD
Robert Justice, MD
Robert Temple, MD
Grant Williams, MD

SPONSOR REPRESENTATIVES PRESENT:

Mohammad Azab, MD, MSc
Eric Edell, MD
Alexander Mancini, MSc

ALSO PRESENT:

Lou Gura
Julia Levy, PhD, DSc
Harvey Pass, MD
Seth Rosenthal, MD

A-G-E-N-D-A

P-R-O-C-E-E-D-I-N-G-S

(1:00 p.m.)

CHAIRMAN DUTCHER: We're going to get started in just a moment if everyone can take their seats please.

Welcome. This is the Oncology Drug Advisory Committee's 54th Meeting. I'm Janice Dutcher. I'm the Chair of the Committee. I'm from Albert Einstein Cancer Center.

We're going to go around the table and introduce the members of the Committee. We'll start with Dr. Ozols.

DR. OZOLS: Yes, Bob Ozols, medical oncologist from Fox Chase Cancer Center in Philadelphia.

DR. SWAIN: Sandra Swain, medical oncologist, Washington, DC.

DR. SCHILSKY: Rich Schilsky, medical oncologist, University of Chicago.

LIEUTENANT O'NEILL-GONZALEZ: Jannette O'Neill-Gonzalez, Executive Secretary, FDA.

DR. JOHNSON: I'm David Johnson, medical oncologist at Vanderbilt University.

DR. SIMON: I'm Rich Simon. I'm a biostatistician at the National Cancer Institute.

DR. MARGOLIN: Kim Margolin, medical oncologist, City of Hope.

DR. RAGHAVAN: Derek Raghavan, medical oncologist, University of Southern California.

DR. KROOK: Jim Krook, medical oncologist, Duluth City Clinic.

MR. GIDDES: Ken Giddes, patient representative.

DR. DeLAP: Bob DeLap, Division Director, Oncology Drugs, FDA.

DR. JUSTICE: Bob Justice, Deputy Director, Oncology Drugs, FDA.

DR. WILLIAMS: Grant Williams, medical reviewer, FDA.

CHAIRMAN DUTCHER: Okay, thank you.

Dr. DeLap, you wanted to make a few comments.

DR. DeLAP: Yes. As I'm sure everyone is aware, we have had some, in the past -- I'm sorry. I thought we were going to have kind of the conflict of interest statement first. Let me restart here.

We're very interested in accommodating all of the public input that people wish to provide at this meeting. We have had, as everyone knows, some people invited to give public input at the behest of

sponsors at past meetings, as well as people who come simply of their own accord to give public input. In order to fully accommodate everyone who wishes to speak, whether they're coming at the behest of the company or simply as a matter of their own volition, we've decided that we would like to organize this by having some additional time attached to the sponsor's presentation which the sponsor may allocate for testimony by patients or other members of the public who wish to come and give their input to the Committee.

So, for this afternoon's session and for tomorrow's session, each of the company's presentations has been lengthened by 50 minutes in order to accommodate people who the company has invited and sponsored to give testimony. So, that will be a separate and additional event to the open public hearing part of the meeting. This is the way we're doing it for this meeting. We'll see how this works and we'll decide how we wish to do it in the future based on our experience.

CHAIRMAN DUTCHER: Thank you.

LIEUTENANT O'NEILL-GONZALEZ: Welcome to the meeting. I'm going to be reading the conflict of interest statement.

The following announcement addresses conflict of interest issues associated with this meeting and is made a part of the record to preclude even the appearance of a conflict.

Based on the submitted agenda and information provided by the participants, the Agency has determined that all reported interest in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions.

In accordance with 18 USC 208(b)(3), full waivers have been granted to Dr. Sandra Swain, Dr. Derek Raghavan, Dr. Robert Ozols, Dr. Kim Margolin, and Dr. David Johnson. A copy of these waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

In addition, we would like to disclose for the record that Dr. Ozols and his employer, the Fox Chase Cancer Center, have interest in Bristol Myers, Squibb Pharmacy, and Upjohn, sponsors of competing products to Photofrin, which do not constitute financial interest in the particular matter within the meaning of a 10 USC 208. Notwithstanding this

interest, it has been determined that it is in the Agency's best interest to have Dr. Ozols participate fully in all matters concerning QLT Photo Therapeutics Photofrin.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. Thank you.

CHAIRMAN DUTCHER: Dr. Temple, do you want to introduce yourself?

DR. TEMPLE: Yes. I'm Dr. Robert Temple, I'm director of ODE I. Thanks.

CHAIRMAN DUTCHER: Thank you.

Okay, we do have time for open public hearing. We did not have anyone request to speak. Is there anyone in the audience who has come to the meeting that does, in fact, wish to make a statement?

Okay, thank you. Then I guess we will go

ahead with the company's presentation.

MS. MANCINI: Thank you.

Good afternoon, Madam Chairman, Members of the Advisory Committee and Members of the FDA. My name is Alexandra Mancini and I'm vice president of regulatory affairs for QLT Photo Therapeutics. We are very pleased to be here today to discuss our supplemental application for Photofrin porfirmer sodium for injection.

Photofrin was first approved in the US in December 1995 for use in photo dynamic therapy which is also called PDT. It was approved for the palliation of certain patients with obstructing esophageal cancer. In February of this year, we filed the supplemental application for use of Photofrin PDT in lung cancer and this will be the topic of discussion today.

Just as Photofrin PDT is effective at palliating obstructing esophageal cancer, it is also effective at palliating obstructing lung cancer. Therefore, the first supplemental indication we are requesting is for the reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobronchial nonsmall cell lung cancer. The primary data we are providing for this

indication comes from two company-sponsored randomized comparative trials that were multi-center, carried out one in the United States and one in Europe, according to essentially identical protocols. We did discuss the protocol design for the US study with the FDA at an end of Phase II meeting.

The second supplemental indication we are requesting is for the treatment of endobronchial carcinoma in situ, or microinvasive nonsmall cell lung cancer in patients for whom surgery and radial therapy are not indicated. Many of the physicians who participated in our palliation trials recognized that Photofrin PDT might be a characterive therapy for early stage superficial disease. However, due to the small number of patients diagnosed annually with such superficial disease, we were unable to carry out randomized comparative trials against surgery.

Therefore, the data we are providing as primary data comes from three investigator-sponsored single arm studies. We have primary data on 102 patients who were treated in these three studies over a period of approximately ten years. We believe that the request for this supplemental indication is very much in keeping with the draft guidelines from the oncology division which encourage supplemental

applications and suggest that possibly alternative sources of data, other than from company-sponsored trials, could be considered adequate.

Today's data presentation will begin with Dr. Mohammad Azab, our vice president of clinical research and medical affairs, who will present the primary efficacy and safety data to support the palliation indication. The primary data for the superficial tumors indication will then be presented by Dr. Eric Edell from the Mayo Medical School, as well as his own experience with the use of Photofrin PDT. Final conclusions will be presented by Dr. Azab.

Also with us today to participate in the discussion period following the main presentations are the three consultants who participated in the review of the patients for the superficial tumors indication. We have Dr. Harvey Pass, a thoracic surgeon from Wayne State University, Dr. Seth Rosenthal, a radiation oncologist from the University of California, San Francisco, and Dr. Howard Sandler, a radiation oncologist from University of Michigan.

At this time, I'd like to invite Dr. Azab to begin the data presentation.

DR. AZAB: Good afternoon, ladies and gentlemen. I would like, in the next few minutes, to

go through the clinical data from the key studies efficacy and safety and the clinical development program in support of the proposed supplemental indication.

As you know, lung cancer is still an important health problem with more than 178,000 new lung cancer cases expected this year only in the US. This makes it by far the leading cause of cancer death. Approximately 20 percent of the newly diagnosed cases present with symptoms or complications of endobronchial obstruction that would require palliation.

The current therapeutic options for the palliation of endobronchial obstruction fall under two broad categories. Those who have a rapid effect on the relief in the endobronchial obstruction, the most commonly method used was the thermal ablation of the tumor using the Nd:YAG laser. That provided the rationale for the use of this comparitor in the two key studies. These modalities, however, do not have any direct cytotoxic effect on the tumor. The other modalities, which are the more standard cytotoxic modalities such as radiotherapy and chemotherapy have a slower effect on the relief of endobronchial obstruction.

The Photofrin photo dynamic therapy, or PDT provides a unique mechanism of action which combines the local effects with a selective cytotoxicity. It's a two-step process which starts by the intravenous injection of a photosensitizer, Photofrin. Two days later, this photosensitizer is selectively retained in the tumor and a light of a certain wave length is directed to the tumor to activate the photosensitizer. That activation will result in a photo dynamic reaction which would lead to a local selective cytotoxicity. The cytotoxicity is achieved by the generation of free radicals which will produce direct tumor kill and a new vasculature shutdown which will result in ischemic necrosis of the tumor.

The clinical development program has supported this indication for Photofrin photo dynamic therapy consisted of the two key studies which looked at the single modality use of Photofrin PDT versus Nd:YAG. And there were other supportive studies including a Phase II dose ranging studies and other studies investigating the use of Photofrin PDT in combination with radiotherapy.

In keeping with the indication that we are seeking today, we are concentrating on the data from

the key clinical studies comparing Photofrin photo dynamic therapy, single modality, versus Nd:YAG thermal ablation. These two studies were both open label, randomized identical design, and they were conducted in patients who are symptomatic due to endobronchial obstruction. The two studies, P17 and P503, were conducted in 35 centers across North America and Europe and included a total of 211 patients.

The protocol defined a Photofrin photo dynamic therapy single course as the injection of Photofrin, two milligrams per kilogram intravenously. Two days later at Day 3 is the application of the light session to the tumor. And then two days later when the photo dynamic effect has taken place and the tumor necrosis is achieved, a debridement clean-up bronchoscopy is done. At that time, if the tumor response is not sufficient, an optional second light session is given.

The protocol also defined the treatment schedule for Nd:YAG single course. In order not to bias the results against the Nd:YAG application and to be consistent with clinical practice, there were no limitations in the number of sessions of light energy dose used for the Nd:YAG single course. The goal was

to ablate all accessible tumors and investigators ended the course only when they decided that there is no further benefit to be gained by further sessions of Nd:YAG. Debridement was usually done in the same bronchoscopy.

The protocol also defined the efficacy endpoints and in keeping with the indication that we are seeking, the relief of endobronchial obstruction was assessed by the objective tumor response through endoscopic assessment of the smallest luminal diameter. The complete response was the classical standard complete regression of the tumor but your response was defined as at least 50 percent increase of the smallest luminal diameter.

Symptom palliation, which is another important goal of the therapy for endobronchial obstruction was a primary endpoint of the protocol. Four symptoms were prospectively identified: dyspnea, cough, hemoptysis and sputum, and they were rated by prospective severity rating scales.

Time to tumor recurrence was a primary endpoint in the protocol. It was later changed to time to local progression to be in keeping with the local effects of the therapy, and also in keeping as a more standard endpoint for the evaluations of

patients with advanced disease. Another time to event analysis was the endpoint of time to treatment failure which, in addition to the local progression reasons, had also failure reasons which are non-local, including any death or any withdrawal from adverse events. The protocol assessment schedule were a week one, month one, two, three and six. All the analysis presented today are the intention to treat primary analysis.

I would like to go through the patients' characteristics from the two studies. They were representative of the patient population of endobronchial obstruction. They were generally consistent across the two studies and they were balanced between the two arms in each of the two studies. Most of the patients in the two studies were men of a median age of approximately 65, a median Karnofsky score of 70. Most of them had squamous cell carcinoma of advanced stage 304 disease.

Many of the patients in the studies had cardiovascular respiratory concomitant disease in addition to their cancer. The majority of the patients of Study P17 had received prior therapy. This was only true in one-third of the patients in Trial P503 because that trial allowed the inclusion of

newly diagnosed cases. Most of the patients had severe endobronchial obstruction. The majority had main stem tumors and the majority had more than 90 percent endobronchial obstruction. That resulted in a very high percentage of atelectasis and that all the patients had one or more pulmonary symptoms.

I would like now to go through the efficacy data starting with the objective tumor response as assessed by the luminal diameter. In keeping with the rapid relief of endobronchial obstruction, most of the patients just received a single course for the relief of obstruction and palliation. That's why we will focus on the course one data, and as I said, using the intention to treat analysis.

These are the data from the week one and month one protocol assessments. The patients who qualified for a complete regression of the tumor, or at least 50 percent increase of the smallest luminal diameter, as you can see here at week one, approximately half of the patients across the two studies had achieved relief of the obstruction after a single course at the one week evaluation. At month one, however, as you can see from the two studies, the response rate was maintained in Study P17 and the same

thing for Study P503 while it declined by approximately one-half for the Nd:YAG arm in both studies. That resulted in a statistically significant different in favor of Photofrin in the two studies.

Most of the other response evaluations at the one week and month one analysis were stable disease or patients who were not assessed. Most of the patients included in this study are at very advanced disease stage and many of them had either death progression or were too sick for evaluation by repeated endoscopic assessments. By month one, about 40 percent of the patients were not available for endoscopic assessment. Beyond month one, more than 50 percent of the patients it's not possible to do endoscopic assessment making any assessment beyond that time point not suitable for forming a comparison.

In discussion of the objective tumor response data, there was a consistency of a higher Photofrin PDT response from two randomized multi-center trials in an intention to treat analysis. Because of the relatively large number of missing data because of the advanced nature of that disease, we've also done an analysis on the evaluable patients only. That analysis confirmed a similar pattern of a higher response rate on Photofrin photo dynamic therapy.

Also, the Agency did a thorough review on the raw data using different response criteria and using the best response achieved by the patient at any time point, or at the certain time point and forward. All of these analyses had the same pattern of a higher PDT response rate.

Another important goal of therapy in addition to opening the luminal, the airways, is the symptom palliation. These bar charts show the percentage of patients who had improvement of the symptoms of the four prospectively defined symptoms in the two studies of Photofrin and Nd:YAG. At week one, there's approximately one-third of the patients who achieved symptom palliation at week one. There was no statistically significant difference between the two arms in the two studies.

At month one, however, consistent with the objective response data, as you can see here, the percentage of patients with dyspnea improvement on Study P17 and Study P503 showed a pattern of a higher response rate for the dyspnea improvement on the Photofrin arm. This difference was statistically significant for Study P503 only. Looking at the other symptoms, there's about one-quarter to one-third of the patients who still achieved symptom palliation by

month one. That difference was not statistically significant in Study P17, and there was a pattern of a higher symptom improvement in Study P503 which was only significant for the cough improvement and the dyspnea improvement.

An important subgroup in the palliation of symptoms is the patients who had severe symptoms at baseline that were probably interfering with the daily activities, so we looked at the month one palliation of patients who had severe symptoms which were a grade 3 or more at baseline. Here, we're looking at the combined data set from P17 and P503, looking at the percentage of patients who had improvement of one grade or more and also, the dramatic improvement of two grades or more in each of the dyspnea, cough, or hemoptysis.

As you can see from the results of Photofrin, this once again looking at each one of these symptoms, there was a consistent 50 percent improvement of all the three symptoms on the Photofrin arm. Looking at the dramatic improvement of two grades or more, there was one-third to one-half of the patients achieving two grades or more improvement from a baseline of severe symptoms. The corresponding figures in this subgroup summary of the Nd:YAG were

consistently lower and ranged from as low as nine percent to as high as 28 percent.

Another way of looking at the evaluation of the benefit risk of the patients is actually to review the individual patients and see, in terms of their efficacy and safety, did they achieve a clinically significant benefit. We've done that through a review of individual case record forms using very rigorous criteria which defined a clinically important benefit by either that the patient achieve a clinically important symptom relief and/or a sustained durable objective response two months or longer. The patient also should have no or minimal adverse events reported and no intervening therapy that could contribute to their positive outcome.

Using these vigorous criteria, we were able to identify 36 patients or 36 percent of the patients on the Photofrin arm who had clinically important benefit. The median duration of benefits using a very rigorous estimation of duration was at least two months after a single course. That estimate is very conservative. As you see the plus here, because actually, there were 23 patients of the 36 who were still at risk in response at the time of the last assessment and some of the patients achieved very

durable clinically important b enefit lasting for more than a year.

This slide summarizes all the efficac y endpoints of the trial from the combined data set of the two studies. This includes also the time to even t analysis, time to local progression, and time t o treatment failure. As you can see here from th e Photofrin PDT, there was a con sistent higher efficacy reported on the Photofrin arm compared to the data on the Nd:YAG. That difference was significant for the objective response at month one, for the sympto m palliation at month one for dyspnea and cough, an d also there was slight difference but it wa s statistically significant for the median time t o treatment failure.

However, the differences -- can I have th e previous slide, please? -- the difference in th e object ive response and in the dyspnea was brough t forward from, was consistent across the two studie s providing stronger evidence of a higher efficacy rate , at least for these two endpoints. This is probabl y related to the cytotoxic effec t achieved by the photo dynamic therapy reaction which does not occur wit h Nd:YAG.

I would like now to go through the safety

results. This will be presented from the combined data overview of all patients who actually received treatment. We will present all adverse events presented by their worst severity and irrespective of whether or not they were related to therapy. Adverse events were collected over the whole follow-up period which is an important point because many of the patients were followed up for many months after the treatment had ended. It is important to look, therefore, at the extent of follow-up for the two arms.

Looking at the extent of the follow-up, more patients on the Nd:YAG had a short follow-up of less than 30 days and more patients on Photofrin had a longer follow-up of more than 90 days. There was also a longer median duration of follow-up on the Photofrin arm from the combined data set. That could introduce a possible bias in terms of adverse events reporting since patients who are followed up for a longer time had the potential of reporting more adverse events related to their eventual disease progression.

Despite that possible bias, looking at the overall safety parameters from the two studies combined in the patients who actually received

treatment in both arms, there was no statistically significant difference between any of these important parameters: Patients who reported at least one adverse event; patients who reported severe or life threatening events, whether that over the whole follow-up period or within 30 days of a treatment procedure; all death from any cause within 30 days of a treatment procedure and withdrawal were all similar and not statistically significantly different between the two arms.

There was also some individual events which are important pulmonary events which were reported at slightly higher incidence in the Photofrin group and we would like to discuss them here. Fatal massive hemoptysis is a rather common complication in patients with end stage endobronchial disease. And the rate of fatal massive hemoptysis in the two key studies that are presented now are the six percent for Nd:YAG and ten percent for Photofrin. These results were not statistically significant.

If we'll look at the non-pivotal studies, the radiotherapy studies -- and this is a compilation of data from several studies. These studies in general compared the combination of Photofrin plus radiotherapy versus radiotherapy alone, and in one

study, Study P504, versus the combination of external radiotherapy and endobronchial brachytherapy. The incidence of fatal massive hemoptysis on radiotherapy alone was eight percent which is very much similar to Nd:YAG and Photofrin in the key studies. The incidence of FMH in the combination arms is 17 and 25 percent, slightly higher than the single modalities.

There are many possible causes of fatal massive hemoptysis that are difficult to distinguish in those patients. Some of them would be due to the tumor progression eroding a pulmonary vessel. Some of them could be treatment induced as the result of the efficacy of the therapy in producing acute tumor resolution, and some of them could be an instrumentation injury. However, the overall incidence in those trials are consistent with the literature and the treatment of endobronchial disease. The incidence of the -- vary from four to 32 percent.

In order to establish a possible or likelihood of relationship to therapy because Photofrin and Nd:YAG are acute therapies with acute effects, we looked at the early FMH which occurred within 30 days of any treatment procedure. Looking at this subset, actually, the incidence is four percent on each arm, identical between the two therapies.

However, recognizing that this is an important event, we have added instructions in the label to contraindicate PDT in patients with tumors that are suspected to erode into a major blood vessel.

Another important life threatening pulmonary event which was reported where there is respiratory insufficiency. These were reported at one percent and five percent for Nd:YAG and Photofrin respectively. These results were not statistically significant.

Once again, using the same convention of looking at the events which were reported within 30 days of treatment, there were three events on Photofrin and one event on Nd:YAG. These events usually are due to a blocking of a major airway by a necrotic debris or mucous plug and can adequately be treated by a clean-up endoscopy and debridement. We have added instructions in the label to mandate a debridement bronchoscopy two days after the light session and also to use caution in treating patients with main airway lesions because these are the patients who would be susceptible when they block their airways to have a severe dyspneal respiratory distress.

Now, looking at the less clinically important but frequent adverse events, this is a list

of all the adverse events in the studies that were reported at ten percent or higher incidence. Most of the events, as you can see, are actually pulmonary events which could be related to the disease progression. There were four type of events which had significant difference and reported at a higher incidence than the Photofrin arm. These are, which is not unexpected, the photosensitivity reactions. There was some increase when we group all the psychiatric adverse events in the Photofrin and also in the dyspnea reporting and in bronchitis.

The psychiatric events were actually almost all mild to moderate and anxiety and insomnia were very transient before or after a procedure and was not of concern. The bronchitis was the same. Almost all of them were mild to moderate and they're probably due to local inflammation which results within seven to ten days after the light application. The other two types of events, photosensitivity reactions and dyspnea carried a slightly higher incidence. I would like to discuss them in the next slides.

Photosensitivity reactions due to Photofrin are usually mild to moderate sunburn-like reactions due to the exposure of the direct sunlight.

These were mild to moderate in the two studies that we reported in 19 out of the 20 patients. Almost all of them were transient and self-limiting. They could be easily prevented by compliance with the label instructions to instruct the patient to avoid direct sunlight during the period of photosensitivity after the drug's injection.

The dyspnea was also reported as a higher incidence in Photofrin and we applied the same convention of looking at the events which were reported within 30 days of any treatment procedure as the ones which are potentially related to treatment. Looking at this group, there was no difference between the incidence in Photofrin and Nd:YAG and most of the difference of the total incidence was as a result of the late dyspnea events which were probably related to disease progression maybe because of the longer follow-up period that we have spoken about earlier.

Finally, in randomized studies, in late-stage cancer patients who are susceptible for serious complications from their disease or from treatment, it is important to look at the survival analysis as an endpoint for efficacy and safety, and as a global measure of the benefit risk to those patients with late-stage cancer. These are the Kaplan Meier curves

and the solid line here is the PDT survival curve which was slightly higher than the Nd:YAG survival curve. That was very comparable. It has a ratio of PDT over Nd:YAG was .82. That was lower than one, but that difference was not statistically significant. The upper limit of the confidence interval was 1.11.

So, in summary, Photofrin photo dynamic therapy achieved the two important goals of treatment in patients with endobronchial obstruction. Relief of endobronchial obstruction was achieved in approximately one-half of the patients. Symptom palliation was achieved in approximately one-third of the patients. There was a consistent pattern of a better objective response than Nd:YAG from the randomized trials. Photofrin PDT was equal or better than Nd:YAG in symptom palliation. Looking with very rigorous criteria at patients who achieved clinically important benefit with no or minimal adverse events, approximately one-third of the patients did achieve that therapeutic benefit.

In terms of safety, the incidence of patients with any adverse events, death within 30 days, the group of severe or life-threatening adverse events as a whole, overall survival and withdrawal was similar between Photofrin and Nd:YAG. The local

effects reported with Photofrin are consistent with its pharmacological action in terms of a transient, inflammatory response or acute tumor resolution. The safety profile of Photofrin PDT is therefore acceptable for the proposed indication.

I would like now to invite Dr. Eric Edell from the Mayo Medical School to present data on the superficial tumors.

CHAIRMAN DUTCHER: Excuse me, Dr. Azab. Can I just ask if we could raise the projector a little bit so that the people on this side of the room can see the slides a little bit better? Is that possible?

Thank you very much.

DR. EDELL: Ladies and gentlemen, it's a real pleasure for me to be able to present information supporting the use of PDT in superficial lung cancer. Before I get into the supportive data, however, I'd like to review with you some of the background information that lead to the use of this therapy at our institution, some of the experience from the Japanese and our institution, and then I'll present data from QLT to support this application.

As Dr. Azab has mentioned, patients with lung cancer have a fairly dismal, overall five-year

survival, and this hasn't changed in recent years. It has been felt, however, that treatment of cancer at its earliest stage offers the best opportunity for long-term survival. It was because of this feeling that the NCI sponsored a multi-center study back in the 1970s in an attempt to screen patients in an early stage, intervene with surgical resection, and then hopefully have an effect on the overall mortality. Those three centers, I think we're all familiar with, occurred at Memorial Sloan-Kettering, Johns Hopkins, and our institution, the Mayo Clinic.

It was during this study that we had the opportunity to learn a little bit more about the natural history of some of these patients. We identified 54 patients during our screening study that were radiographically occult. These were picked up by sputum cytology. In that category of patients, 11 were bronchoscopically occult and nine of those patients underwent a pneumonectomy to control the disease. But it was those 11 patients that were bronchoscopially occult where we first started using a hematoporphyrin derivative which is a less purified form of Photofrin as an aid in localizing these cancers. It was quite helpful and these patients went on to treatment.

We also found that these patients are at a higher risk for developing a second cancer at a rate of five percent per year. As I mentioned, some of them have large operations such as pneumonectomies to control their disease. So, we felt if these patients were returning that we needed a treatment that would preserve lung tissue. This is what lead to the use of photo dynamic therapy at our institution in treating these non-surgical patients.

The Japanese have the largest experience in the world treating superficial cancers with photo dynamic therapy. They've been doing this since 1980. They reported over 251 patients that have been managed with this therapy. This was initially done with a hematoporphyrin derivative as in our institution, but later, they've been using Photofrin PDT. In early stage cancers, they report 95 patients and a complete response rate of 81 percent with a recurrence rate of approximately 16 percent. Some of this information was presented and lead to the approval of Photofrin PDT in Japan in 1994.

Now even though we have a smaller experience at our institution, I think the results are fairly similar to those of the Japanese. We, too, treated our first patient in the later stages of 1980.

Since that time, we've treated 58 non-surgical patients with early superficial cancer. We have a complete response rate of approximately 84 percent. Our recurrence rate after a single treatment is 39 percent with a median time to tumor recurrence of 4.1 years. After a second or more treatments, our recurrence rate dropped to 22 percent. We have a median survival of three-and-a-half years.

We became very encouraged about the opportunity for this treatment to control these very early superficial cancers and we extended our indication at our institution into two protocols. We now have not only a protocol for non-surgical patients, but we also have a protocol for surgical patients with superficial cancer to be managed with photo dynamic therapy. These are patients who are initially treated with photo therapy in a single arm fashion. If they have a complete response, they are then followed until recurrence or about two years or more. If they have a less than complete response or recurrence, they go on to surgical resection. We recently reported our first 21 patients. This summer we had a complete response rate of 71 percent and a recurrence rate after a single PDT of 19 percent.

But I'd like to now turn and present

information, the data from QLT to support an indication for the treatment of endobronchial carcinoma in situ of microinvasive nonsmall cell lung cancer in patients for whom surgery and radiotherapy are not indicated. So, a very conservative group of patients. The data to support this indication came from three open label, single arm studies. At least four investigators that had been involved with the palliation studies decided on their own that they wanted to try photo dynamic therapy in a curative intent. So, these were investigator-sponsored trials. They occurred in three different series that you see here.

They identified 102 patients that were treated over 10 years. The tumor stage included carcinoma in situ, T1, T2. There were no N1, or metastatic lesions identified. No nodal involvement or metastatic lesions identified. The majority of these were radiographically occult. The patients were considered inoperable by both the referring physician and the treating physician. Some, however, may have been eligible for radiotherapy. That was not an exclusion criteria and therefore, could have participated in comparative radiotherapy trials.

It was because of this that QLT decided to

try and select a subset of patients for whom radiotherapy and surgery were not indicated. In order to determine the eligibility for radiotherapy and surgery, they sought the outside advice of three experts: two radiation oncologists, Drs. Rosenthal and Sander, and a thoracic surgeon, Dr. Pass. After collecting the information from these consultants, they developed a subset of 24 patients that made up the subset that you see in the document.

This slide shows why surgery and radiotherapy were not indicated in that subset of patients. Poor pulmonary function was a problem for the majority of these -- for a lot of these patients. Multi-focal or multi-lobular disease precluded surgery in 21 percent and created a field that was unacceptable in over a third. Prior high dose radiotherapy was seen in almost 40 percent of these patients. The data from this subset, in addition to the data from all patients treated, have been used together to support the indication for the treatment of superficial cancers.

The majority of patients were men with a median age of 60. As could be expected by the selection process, the indication group had more prior therapy, a lower or worse FEV_1, and they had more

multiple tumors. The vast majority had very early squamous cell carcinoma and 80 percent were confirmed radiologically occult. This slide just shows that this group of patients were not -- their tumors that were used were not isolated tumors. In the indication group, 71 percent of those had had a previous lung cancer and 55 percent of those in the total group had had previous lung cancer. Some of these cancers were late stage. This may have had an effect on some of the survival statistics.

The measurements of efficacy included histologic complete tumor response, time to tumor recurrence, survival and disease-specific survival. The efficacy results for the total group are based on 100 patients rather than 102 because at the time of treatment, two patients -- they were unable to confirm the presence of tumor. If you see, also, it's important to note that the complete response definition was based upon the individuals' investigators. Those investigators decided that the time after treatment to establish a histologic complete response was determined by them, not the protocol. The complete response rate was quite good in both groups. The confidence interval was also quite tight, and this occurred primarily after a

single course of treatment.

In those patients who achieved a complete response, close to 50 percent had recurred at the time of the last evaluation. This gave a median time to tumor recurrence of 2.7 and 2.8 years. The upper limits of confidence intervals couldn't be calculated because some of these patients had not recurred at the time of last evaluation. This Kaplan Meier curve just shows the consistency between the two cohorts. The five-year survival estimated from this Kaplan Meier curve in both groups was approximately 50 percent. When you look at death from cancer, the median survival increases, as you would expect, and the disease-specific survival in both group approaches, 55 to 60 percent. Note that the X axis is out in years and not months.

The FDA raised a couple of points regarding the analysis of the efficacy that I'd like to address now. As I previously mentioned, if you looked at the complete response rate as assessed by these investigators in the 100 patients used for efficacy, the time of histologic confirmation was determined by the investigators and sometimes, this was quite short after the initial treatment. If one were to take a biopsy to confirm histologic complete

response at three months or greater, the number of complete responses would go from 79 to 46. If you use an n of 97 which excludes three patients who had different histology than nonsmall cell lung cancer, carcinoma in situ, blastoma, those sorts of things, then you would get an overall complete response rate of 47 percent. The median time to tumor recurrence, however, could not be calculated. In fact, at three years, only 30 percent of these patients had recurred. So, with this analysis, you do see a decrease in the efficacy, but maybe a higher quality of patients in that the duration of response appears to be longer.

A second point that the FDA requested was to show the survival based upon the T stage. This slide shows that Tis and T1 survival statistics are very similar with four-year survivals in the 45 to 55 percent range. If you look at disease-specific survival by T stage, we also have similar results between these two groups.

The safety of this treatment was based on all patients, in all 102 patients seen. At least 50 percent had one adverse event. There were 11 percent that had severe or life threatening events. Six of these recurred within 30 days. There was one death within 30 days. This patient died of a fatal massive

hemoptysis. But it should be noted that this patient had previously received bilateral upper lobectomies and had also received interbronchial radiation therapy in the treatment zone. There were also a couple of patients outside this 30 days that died of fatal massive hemoptysis. These patients had recurrent disease and died somewhere between a year and three years after their treatment.

If we look at those six patients that had severe or life threatening events within 30 days, two of these patients were due to severe sun photosensitivity. The other four had severe dyspnea with or without cough. In two of these, it appears that the light dosage exceeded that which is recommended. One other patient had two lesions, one in each main stem bronchi that were treated concurrently. This may have been avoided if these were treated on separate occasions. There was an individual who had a sole remaining airway where his lesion was treated.

The most frequent adverse events are summarized in this slide. Photosensitivity reactions being mild were of the highest number seen. Similar to the palliation studies, these were primarily mild, and face burns. In the category of mucositis, there

were exudative obstructive lesions, edema scene . These were all around 20 perce nt. These could all be explained based upon the pharmacologic effects o f phototherapy. And the importa nt thing is that all of these were reversible and didn't cause sever e problems.

I think that to summarize, if you firs t look at the efficacy of photo dynamic therapy , Photofrin PDT in the management of superficial cancer , the efficacy looks quite encou raging. If you compare both the three studies that were given by QLT i n addition to the FDA method ana lysis and those that we have seen with historical data, 47 percent in thi s population of people still shows good efficacy.

More importantly, the median survival of these patients is consistent t hroughout these studies that I've reviewed. I think also that the safety dat a would suggest that the safeness of this treatment is also reasonable. With that information, I think it i s reasonable to conclude that Ph otofrin PDT is safe and effective therapy for the treatment of carcinoma i n situ or microinvasive nonsmall cell lung cancer i n patients for whom surgery and radiotherapy are no t indicated.

Thank you for your attention.

DR. AZAB: Thank you.

So, in conclusion for this supplemental indication of Photofrin PDT in lung cancer in the palliation indication, we believe there are two adequate and well controlled studies that demonstrated the efficacy and safety for Photofrin PDT and the palliation of interbronchial obstruction. In the superficial cancer, there are three independent studies and a literature review provided consistent evidence of the efficacy and safety of Photofrin PDT in the treatment of those early cancer patients with no other alternative standard therapeutic options. Thank you very much for your patience.

CHAIRMAN DUTCHER: Thank you very much.

Questions now from the Committee for the applicant?

Dr. Schilsky?

DR. SCHILSKY: Well, I guess I'll start off with a few questions. I'm just curious with respect to the pharmacologic effect of Photofrin, you mentioned that there is a selective uptake in tumor tissue.

DR. AZAB: Yes.

DR. SCHILSKY: So, I'm curious to know, is it possible to estimate the magnitude of the

difference between tumor tissue and normal tissue with respect to uptake of the Photofrin?

DR. AZAB: Okay. Selectivity is usually achieved by the association with the low density lipoproteins, the LDL. Many of the cells which have actually expression, high expression of LDL receptors have expressed that selectivity. That's why the proliferating tissues such as the tumors and the endothelial cells and the blood vessels also have a certain selectivity of the photosensitizers. That brings the selectivity in the tumor and the new vasculature shutdown mechanism.

In terms of the magnitude of the difference, I believe probably if Dr. Julia Levy, who is the chief scientific officer and has done many of the basic pharmacological work, probably could have further comments.

DR. LEVY: Yes, that's a very interesting and important question because --

CHAIRMAN DUTCHER: Could you just state your name?

DR. LEVY: Oh, I'm Julia Levy. I'm the chief scientific officer and chief executive officer of QLT.

The question as to detection of the ratios

of drug in tumor versus normal tissues is a question that is raised frequently by people interested in this technology. You can get a rough estimate of relative concentrations by using the endogenous fluorescent characteristic of these photosensitizers. By using certain kinds of emission, you can get a fluorescence detection.

However, what I would like to add to that is that this actually creates information that may not have relevance in terms of the efficacy of the treatment. As Dr. Azab has mentioned, there are two mechanisms of tumor cell destruction and this has been well documented in pre-clinical work with Photofrin that the concentration of the drug not only in the actual tumor cells, but also in the endothelial vasculature of the neovasculature are both equally important in terms of the efficacy of the elimination of the tumor. For this reason, when you do a simple measurement basically measuring the concentration within the tumor, you may not be getting a good measure of efficacy because of the vascular effect.

DR. SCHILSKY: Okay. Let me go on to a few questions about the studies. I'm a medical oncologist so I don't do bronchoscopies and things, and so I had a few questions.

It wasn't clear to me in the two studies, what was the medical specialty of the physicians who were doing this? Was this done by thoracic surgeons? Was it done by pulmonologists or others? And what was the relative skill level of the physicians, particularly with respect to use of the YAG laser?

DR. AZAB: Yes, that's a very good question. Actually, in that respect, most of the studies since Nd:YAG was an established therapy and PDT is an experimental therapy, in order to identify the centers to participate in the trial -- especially the trials against YAG -- actually, all of the centers were centers who had the equipment, who were using an experienced in the Nd:YAG thermal laser ablation. Some of them did have some experience in PDT, but many of them did not have experience in PDT. So, if there is any possible actually sort of shift of experience, it was probably more on the Nd:YAG because that's how they were selected.

And you're absolutely right. Actually, it was the investigators in terms of specialty, were either thoracic surgeons or pulmonologists. These were the two specialties in --

DR. SCHILSKY: But you're satisfied that they all had some comparable level, basic skill level

and experience with using the YAG therapy?

DR. AZAB: Yes, they were all chosen -- one of the criteria of the choice of these centers was their level of experience with Nd:YAG. So, that was a major -- selection.

DR. SCHILSKY: I guess that leads into my next question. I'm a little confused as to why the results with the Nd:YAG, particularly at one week, why they're not better than they are in these studies. You know, I enjoyed watching this video that we received and the one thing that was clear is that when you go in there with that laser, you just sort of laser everything out and you get to chart up a bunch of tissue, you know, and that's that. Whereas when you do the photo dynamic therapy, you don't see any immediate vaporization of the tissue.

DR. AZAB: Yes.

DR. SCHILSKY: So, in the study design, since the physicians could basically apply the YAG laser as often as they wanted, it would seem to me that virtually all the time that there should be complete resolution of the tumor at least at one week. That clearly is not the case in the data that you reported.

DR. AZAB: Yes, this comes from the two

sets. I'll probably explain why because I think that's a very good question.

Can I have slide 268 please?

The use of the thermal YAG -- it's true that you can do ablation of the tumor but there is a limit of how far you can apply it because of the very high risk of damaging of the normal tissue because it's not selective and also it 's a very high skillful technique. This is just an illustration of how the tumor ablation is achieved. With Nd:YAG it's a high energy thermal beam so it is true that it cuts through the tissue into ablation. However, you can only treat the exophytic tumors, and also you have difficulty treating the circumferential tumors because you have to apply the laser at several points.

Also, you have to be very careful in not approaching the bronchial wall because if you approach any normal tissue of the direction of the laser, is in the wrong direction, you could have a perforation of normal tissue. So, there are limits of the use of the laser in terms of how far you can ablate the tumor without producing damage. These sort of things were, of course, very important because all these people were very experienced with Nd:YAG. As I said, there are 35 centers from North America and Europe.

PDT, however -- this is just a n illustration of a tumor and it also doesn't give the full impression because the circumferential tumor , when you introduce the fiber o ptic and then shine the light, the light will be addressed to the whol e circum ference of the tumor. The light will have a penetration of about five and eight millimeter in the tumor so you can actually treat most of the depth of the tumor in a circumferential way through the whole length with just switching on the lights of the fiber optic. It does not require the same skills, it does not have the same limitation o f how far you can apply the YAG laser. This stars, of course, all the areas which have the light and will have the photo dynamic reacti on and will result in the cytotoxicity to th e tumor.

DR. SCHILSKY: Okay. So, another questio n then. When looking at the one month complete respons e rates, so, again, it's a littl e unclear to me why the results with the YAG therapy have deteriorated so muc h by one month, whereas the results with the PDT seem t o be preserved at one month. Do you just attribute tha t to the rapid regrowth of the local tumor over tha t short period of time?

DR. AZAB: It has been reported in all th e

physical methods -- some peopl e also have said of the thermal ablation, they could go with the bronchoscopy , do coring out and actual mecha nical debridement. But also, there's a limit of how far you can go withou t damaging. So, most of the phy sical effects, yes, you can remove tumor and you can introduce removal o f pieces of the tumor, but there are no cytotoxi c effect. Most of the literature data and all th e physical methods show that there is a rapid regrowth because you are not altering the dynamics or th e kinetics of the tumor itself. You're just physically destroying the tumor.

I think perhaps some of our experts -- Dr . Pass had a lot of experience with PDT. Probably h e could explain why this is logical.

DR. PASS: Yes, this is not a unusua l phenomenon if you compare these two. Indeed, on e month is enough for regrowth after YAG. But because of the cytotoxic reaction that's actually occurrin g over a period of time and because you probably ar e able to get a more controlled endoscopic obliteration of the tumor and that effect continues for a time , it's not unusual at all to see this persistence of th e photot herapy effect compared to the YAG and othe r core-out methods.

DR. SCHILSKY: All right, so that sort of makes sense. I'm trying to get all these various pieces of data to at least add up in my own mind. If all that is correct, then I'm not clear on why, in fact, there are no differences in time to local progression between the two arms. Because it would seem like if the tumors have grown back quickly after the YAG therapy, that there should be a shorter time to local progression and yet, your statistical analysis didn't demonstrate that.

DR. AZAB: It is probably because of the definitions of the time to local progression and the time to treatment failure in the studies. I think it is a fair comment that probably the definition in the protocols was not adequate. The time to local progression was not a simple time to objective progression of the tumor as you would apply in many of the oncology studies. It was actually a composite time to event analysis. The events were either tumor progression or increase in the symptoms of the patients at any time. And also, this analysis is also compounded by all the failure of patients who were either not assessed or who were not available for assessment.

So, it does not look at the group of

patients who had the benefit if you look at the whole group. And also, because it's a composite time point, not just the objective progression that has a subjective element to it of -- symptoms as well. It was very difficult. I think there was a concurrence between us and the FDA in terms of the usefulness of these times to event analysis by the definition in the protocol which I agree, was not optimal.

DR. SCHILSKY: I just have one more question. I guess I'm still a little confused as to whether, after PDT therapy, patients had an improvement in their dyspnea or not because in your response data, in your efficacy data, you demonstrated that there was improvement in dyspnea. And yet, there's also an increase in the adverse event reporting of dyspnea following PDT. So, are they breathing better or not?

DR. AZAB: Well, as you well know, there are two very different endpoints -- the dyspnea and also the same thing from the review of the FDA -- that are looked at as an efficacy endpoint, because that was regularly assessed using prospective scales at certain time points. So, that was the best way to look at it. The adverse events, as I said, were irrespective of whether they are related to the tumor

or not. And they were collected during the whole follow-up period of the study. So, a patient three or four months, or six months after receiving a treatment reporting a dyspnea because he was still under follow-up on the PDT arm, it would get captured.

So, if you look at the dyspnea events within 30 days, they are very similar. It's 16 percent and 11 percent. Both Photofrin and Nd:YAG have local effects which are acute. Beyond 30 days from a treatment procedure, it's unlikely that these events were related to therapy, and that's where the difference comes from.

DR. SCHILSKY: Thank you.

DR. AZAB: Yes?

DR. MARGOLIN: I have two questions, sort of technical questions. One is, who provided the equipment and maintained and assessed the quality of the equipment for both techniques? The other question is whether your stance is that the apparent ease or possibly improved safety, at least for some patients, of the PDT therapy over the YAG therapy is expected to increase the number of practitioners who can offer this procedure to a larger number of patients?

DR. AZAB: In terms of the equipment, I'd like to ask Lou Gura, who has been part of these

studies and their conduct.

DR. GURA: Yes, my name is Lou Gura.

With regard to the first part of your question, the equipment, the actual laser companies that provided the lasers. The YAG lasers were commercially available at that time, so they were a part of a commercial operation. They were maintained at the hospital, the units where they were, by the companies that provided them.

With regard to the PDT lasers, they were experimental at the time. They, in fact, were provided also by laser manufacturers. But the company maintained or insisted on calibration and follow-up to ensure that they were, in fact, running to standard. We had power meters there to ensure that the light was being delivered at the proper wave length and of the proper power. So, there were two different things. One was commercial, one was R&D. We augmented the R&D ones to assure reliability.

DR. AZAB: All the studies had the -- of calibrating the wave length and the light power, which are the two most important parameters for the light. Those were collaborated by the power meters supplied by the manufacturers of the laser devices.

In terms of the application of the

therapy, I mean, we're hoping to be able to provide another alternative modality for the therapy of these patients for the palliations of interbronchial obstruction. It is very difficult to answer how would that be? I think there will always be the fact that people specialized in that technique were either thoracic surgeons or pulmonologists that should apply the therapy because you have to have the experience in bronchoscopy in order to be able to do the therapy. The appropriate training, of course, the procedures would take place. Photofrin is available on the market for esophageal cancer and there are training procedures there as well.

Yes?

DR. RAGHAVAN: I also have a technical question. Could you talk a little bit about dosimetry? You've talked about calibration. When we look at the data that you've provided, I guess the dose in joules is quite variable. So, what are the indices for total dosage, time of delivery? How do you standardize the approach that Dr. Pass might have in Detroit, versus Dr. Edell in Rochester? All of those sorts of things.

DR. AZAB: Okay, the approach in terms of the procedures was actually very in detail, described

in the protocol and followed by the practitioners. As you rightly said, there are various factors. Actually, the light dose is fixed. The light dose, depending on the fiber you're using, if it's for the long tumors, it is 200 joules per centimeter. Using the cylindrical diffusers if you have a long tumor. If there's a fixed point of a tumor that does not involve the whole circumference, then you use the microlens fiber. Most of the patients had longitudinal tumors and had the 200 joules per centimeter. So, that was a standard dose. It was also applied with the same power at the same fixed time. It was approximately eight minutes and 20 seconds. That was the application of the light which would provide the 200 joules per centimeter.

The equipments were all calibrated to provide that power, and also to provide the light with the wave length that would activate Photofrin, which is 630 nanometers. So, we believe, in terms of the practice and the dosimetry of the light, that all the criteria were detailed in the protocols. The investigators were required to be trained on the procedure before they start the indication.

CHAIRMAN DUTCHER: Dr. Johnson?

DR. JOHNSON: I have actually several

questions, some that were generated by the presentation.

It wasn't clear to me in reviewing the material provided by yourselves, the symptom relief was assessed by the physicians treating the patients?

DR. AZAB: Yes, that's correct.

DR. JOHNSON: Was any effort --

DR. AZAB: By asking the patients -- using the perspective scales, using the severity rating scales and the protocol.

DR. JOHNSON: Was any effort made for the patient to self-assess their symptoms? In other words, using the symptom assessment scale, as an example?

DR. AZAB: It was not a self assessment scale. It was the severity rating scale that was provided in the protocol. The investigator would ask the patients questions to evaluate their symptom improvement.

DR. JOHNSON: But ultimately, it was the physician treating the patient who determined that the patient's symptoms had improved or not?

DR. AZAB: Well, I mean, ultimately, that is correct. The patient describes the -- the condition in terms of how they rate according to the

scale. Because they were asking specific questions and they go through the scale, and they were identified how much improvement they had or not. That's correct.

DR. JOHNSON: While you're looking for a slide --

DR. AZAB: Okay, it's just the scales, yes.

DR. JOHNSON: -- let me make myself very clear. I know the scale.

DR. AZAB: Yes.

DR. JOHNSON: I just want to make the point very clearly that there's a difference between a physician asking a question and then recording the data, and asking a patient to self assess him or herself, the status of a symptom.

DR. AZAB: You're absolutely correct.

DR. JOHNSON: And that did not occur in this study, is that correct?

DR. AZAB: No, it was not a self assessment. That was a scale provided in the protocol and the investigator had to ask questions to provide the rating. That is correct.

DR. JOHNSON: Do you want to comment?

DR. AZAB: It's the scales.

DR. JOHNSON: Under Slide 33 you mentioned life threatening pulmonary events and you made a point. I would like to really concentrate on the Phase III data. You combined the data of P17 and P503 and you note that fatal massive hemoptysis occurred in ten percent of patients in the se two studies, and six percent in the YAG.

On the next page in slide 35 you mentioned that there's a difference in life threatening pulmonary events which you've characterized as respiratory insufficiency. I'm not exactly sure I know what you're trying to say there. But if one combines the incidence of life threatening events, not separate them out as has been done here, you have a 15 percent instance of life threatening events on the PDT and seven percent on the YAG arm. Is that correct?

DR. AZAB: That is correct.

DR. JOHNSON: Is that statistically significant? Is it clinically different?

DR. AZAB: I would ask our statisticia n for that?

Yes, it's actually not statistically significant. I think that when we present the life threatening events as a whole, we've done the analysis and that was not statistically significant.

DR. JOHNSON: Okay. My guess is it may be but you say no. So, we'll hear about that later.

DR. AZAB: Can I make a comment?

DR. JOHNSON: Yes.

DR. AZAB: Yes. It is true that most of the pulmonary events -- just I'd like to explain. Many of these pulmonary events, these are patients with an end-stage endobronchial disease and it is very difficult to differentiate what is due to the natural history of the progression of the disease and due to treatment.

As I said, these are acute treatment effects and probably the best way of looking at it is to look at the events that occurred within 30 days, which is the likelihood of the event to be traded to treatment. And actually, if you look at within 30 days, there are four patients on the Photofrin with FMH and three respiratory insufficiency, and there were one and four. So, that makes seven on Photofrin and five on Nd:YAG. So, actually, within 30 days, even if you combined them, that difference is seven percent and five percent.

You're absolutely right, those under respiratory insufficiency, it was, actually, a compilation of terms. They were reported as either a

severe dyspnea, or a bronchia spasm or a hypercapnia. These were usually, as I said, if they are related to treatment, then that's probabl y the case in the three events which happened within 30 days. They are due t o a necrotic material blocking an airway in a lesio n which was in a measured airway.

DR. JOHNSON: How many of these patients underwent post-mortem examination, if any?

DR. AZAB: The patients in the respirator y insufficiency was only one patient for the death. Th e respiratory insufficiency, these patients did not die . In the FMH patients, I don't think that we hav e atoxic examination from the patients -- as I said , many of the patients with FMH died more than 30 days after treatment procedure. The four percent on each arm who died within 30 days did not have atoxic.

DR. JOHNSON: Okay, moving to you r material you provided to us -- I'm going to skip over several things. I think they've already bee n discus sed. I was curious on page 78 of you r submission, specifically talking about the curativ e group with the early stage disease which --

DR. AZAB: Which page?

DR. JOHNSON: Page 78.

You had mentioned to us the fact tha t

these were patients in your so-called indication group that your expert panel had determined were not candidates for radiation therapy or surgery. Yet, I find out that seven of these patients subsequently received radiation therapy upon progression after PDT. That's seven out of 24, two of whom received external beam radiation, I believe. Or, I'm sorry, six of whom received radiation therapy, two of whom received external beam radiation; four of whom received endobronchial -- brachytherapy.

How do you reconcile those figures?

DR. AZAB: That is correct. That's a very good question. Actually, there's a simple answer to that. As you can see here from the 24 indication patients who had subsequent therapy, none of them had any surgical procedure which confirms the ineligibility to surgery.

In terms of the radiotherapy, most of the patients actually had -- these were patients who recurred, who already were not indicated for surgery or radiotherapy, and recurred after PDT. Most of them received these radiations as palliative, not as a curative intent. So, they were contraindicated for surgery and radiotherapy for a curative intent. As you can see from their survival, actually, all of them

except one or two had survival less than one year or six months. So, they received these treatments as palliative doses of radiotherapy.

DR. JOHNSON: Okay, thank you.

Now, on page 82 of your presentation, you indicated that there's a high risk of ulceration with tracheal or main stem lesions. I wanted to know if any of the ulcerations that occurred in this group of patients occurred in your 24 indication patients? You went back and forth in your presentation between the total group of patients when talking about adverse events, and to the indication patients often when you were talking about efficacy issues. But you did not break out, at least to my satisfaction, the differences in adverse events in that 24 group.

DR. AZAB: Okay. Adverse events were quite comparable in the two groups. You're absolutely right. I'd like to first address the question in terms of the ulceration. They were all mild and superficial. They were not of concern in these trials.

Could I have slide 366, please, which actually details these events?

Most of these events were due to the pharmacological local effect of PDT. This slide shows

the indication versus the non-indication patients in terms of all their respiratory events. These are the indication and these are the non-indication. As you can see, if you lump all the respiratory events for these patients, they are quite consistent. If you look, for example, I don't think that the ulceration is here. Actually, in the indication, there was none of them that had the superficial ulceration and nine of the 78 non-indication patients had the superficial ulceration. All of these were reversible with the healing of the tissues after the pharmacological effect.

DR. JOHNSON: Okay, leave that there just for a moment.

DR. AZAB: I'll leave it here.

DR. JOHNSON: You may answer some of my other questions.

DR. AZAB: These are subgroups of the patients. These are not perspective comparison of the indication. This is the retrospective grouping of the indication versus the non-indication. So, we did not do any formal statistical comparisons there.

DR. JOHNSON: Okay. Also on this page, you mentioned the fact that there were 11 patients who experienced life threatening adverse events.

DR. AZAB: Yes.

DR. JOHNSON: You mentioned that there were three patients that experienced life threatening dyspnea which required emergency medical treatment, including tracheostomy.

DR. AZAB: Yes.

Can I have slide 354?

These are all the life threatening events which occurred within 30 days of a treatment procedure. Two percent of them was actually photosensitivity, but slightly severe sunburn and they were still reversible. Four patients --

DR. JOHNSON: Excuse me. Wait just a minute.

DR. AZAB: Yes?

DR. JOHNSON: You characterized as a slight sunburn severe and life threatening?

DR. AZAB: No, no, no. No, no, severe -- yes, the terminology that was used in the trials was severe and very severe. So, all the photosensitivity reactions when they happen in a very severe form -- and these two patients particularly had some physical erythema and vesiculation, so the investigator characterized them as very severe. In the protocol, very severe -- here, we used the -- very severe as

life threatening.

So, actually, I think it's a problem of terminology. These were reported as very severe photosensitivity reactions. None of these patients died or had any long-term sequelae or skin graft in any sort of life threatening way. They were just reporting a sunburn photosensitivity which the investigator noted as very severe. In our terminology, we used very severe as life threatening, but it's a problem of terminology.

Oh, okay, I have actually discovered that these were, as you see here, it's a severe/life threatening. So, these actually are reported as severe, not very severe. So, I'm sorry about that.

The ones who were reported were severe dyspnea. These were reported in four patients and as Dr. Edell went through the presentation, all of them are more-or-less predictable from the -- if you look at these four patients, two of them received an overdose of the light. These were investigator-sponsored studies, so we did not have the same control that we had on the key studies and the palliation.

So, two received an overdose of light and two patients were -- one of them were treated and both main stem had two lesions and treated with both main

stem lesions at the same time. So, with the inflammatory response, it was predictable that he would get that severe dyspnea. If they were treated sequentially, that could have been avoided. And the other one had a pneumonectomy before and had a one sole remaining airway and was treated on one on the remaining airway.

I just wanted to mention that these patients -- 70, as Dr. Edell mentioned -- 75 percent of these patients in the indication had prior lung cancer, probably at the higher stage when they entered the trial and they had exhausted several other therapies. So, they were not the newly diagnosed or newly screened early cancers.

DR. JOHNSON: So, you had proposed to exclude them from your indication? Is that what you're suggesting?

DR. AZAB: The indication excludes the patients who are candidates for surgery and radiotherapy.

DR. JOHNSON: No. No, no. You are trying to make a case for yourself by saying that these had been patients with previous cancer, lung cancer, and therefore had had previous treatment.

DR. AZAB: Yes.

DR. JOHNSON: I understand that. Are you suggesting that's the reason that they should be excluded from the indication for PDT?

DR. AZAB: Oh, no. I was just making the point that they have other high risk factors in having the multiple --

DR. JOHNSON: Right.

DR. AZAB: -- and prior treatments, as I said.

DR. JOHNSON: Right. Okay, we understand that.

DR. AZAB: Thank you.

DR. JOHNSON: So, I'm still unclear in my mind, why would two people receive an overdose? Was this just simply a physician error?

DR. AZAB: Yes. It was -- yes, I mean, we can show the slide showing the history of that particular patient. As I said, these are investigator-sponsored trials that we collected the data for. So, if the investigator decided for that lesion at that time that we'd had a light dose --

DR. JOHNSON: So, it wasn't an equipment error or something of that nature?

DR. AZAB: No, no, no. That was a physician. This is the patient with the light

overdose. He had six overlapping light doses. On e site got four times the usual dose. He had just - - the inflammatory reaction was exaggerated. And even with that light dose which was very high, th e inflammatory action was the fibrin plug durin g treatment. This resulted in a severe dyspnea because it blocked the airway, but resolved through sten t placement and the patient recovered.

DR. JOHNSON: Okay, thank you.

DR. AZAB: Thank you.

Yes, please?

DR. SIMON: A couple of questions. On th e palliative patients --

DR. AZAB: Yes.

DR. SIMON: -- the symptom assessment . Was there any producability evaluation of th e assessability, evaluation of symptoms by th e physician?

DR. AZAB: I'm not sure I understand the question.

DR. SIMON: Well, you said that th e evalua tion of symptoms was based by the physicia n asking the patient --

DR. AZAB: Yes.

DR. SIMON: -- "is your cough improved?"

Was that done in duplicate to see that you get the same answer when two different people ask the same patient?

DR. AZAB: Oh, no. There was not. The cough, in terms of improvement, that was not the simple question. It was questioning through the scale that we've provided. The improvement was defined as at least one grade improvement in that scale.

DR. SIMON: How was that done physically? Was that done by handing the patient a piece of paper and filling it out?

DR. AZAB: No, that was by direct questioning during the consultation.

DR. SIMON: So, for a symptomatic evaluation, there's no reason to believe that that's reliable in any way, I would think, particularly if the questioning is being done by the physician who is an expert in that particular modality of therapy?

DR. AZAB: Well, the physicians, our experts, were mostly chosen because they were experts in the Nd:YAG. Actually, Photofrin PDT was an experimental modality for them. So, it is true -- you're absolutely right -- this is an open trial and these symptoms are prospective scales that could have the subjective evaluation. We always struggle to --

we know that in cancer patients, it's very important to demonstrate therapeutic benefit to the patients. And the therapeutic benefit to the patients, sometimes we struggle with the objective response -- what that means if the tumor shrinks or not, although it is objective. One of the ways is to look at the symptoms.

So, it is certainly not ideal because it is subjective in a way, but it was at least provided in a prospective scale. But I acknowledge your point.

DR. SIMON: My other question involves the patients with superficial lesions.

DR. AZAB: Yes?

DR. SIMON: You've identified an indication subset of patients who were not suitable candidates for radiation or surgery. And with the radiation we're talking about now was curative dose radiation. What is the dose with curative intent, the dose of radiation, to an in situ lesion?

DR. AZAB: We used the expert radiation oncologist to provide with the evaluation of the patients.

So, Dr. Rosenthal, would you like to address that question?

DR. ROSENTHAL: I think that's a difficul t

question because there are --

I'm Dr. Seth Rosenthal from Sacramento.

That's a difficult question. There is a large experience using radiation for invasive T1 lung carcinomas. In that situation, a curative dose is on the order of 60 to 65 gray. There is experience using radiation for carcinoma in situ in other sites, on the larynx and the cervix. In those situations, shorter doses are in the range of 60 range. However, you are correct that there are not any large published series of curative radiation for Tis of the trachea l bronchial -- of the bronchus.

DR. SIMON: What was the subsequent palliative dose radiation? What doses were given to these patients, the indication set of patients?

DR. AZAB: In the page that was provided in the ODAC documents, some of them had actually the number of grays in the table that Dr. Johnson referred to. It's about 20 gray. That was the doses used for the palliation afterwards. Actually, in terms of the concentration, there is a debate, actually, in the literature that the Tis -- radiotherapy is probably not a standard treatment for Tis because of the absence of curative survival data following radiotherapy in Tis patients because they are very

rare.

DR. SIMON: Thank you.

DR. AZAB: Yes?

DR. MARGOLIN: Well, I'm not sure if you provided it and I missed it, or if you didn't provide it -- what the breakdown was between the two modalities: the YAG laser versus the PDT among individual operators? In other words, at the centers that had the larger numbers of patients, was there some kind of block randomization to make sure that the same person was doing approximately equal numbers of procedures? You didn't have, you know, Dr. X doing all YAGs and Dr. Y doing all PDTs?

DR. AZAB: No, no, they were stratified. You're right. They were stratified by center, so in the center that these -- the blocks were of the block size of four and in all of the centers after four, they would be balanced. In each center they would have two YAG and two PDT patients.

CHAIRMAN DUTCHER: Dr. Temple, do you want to say something?

DR. TEMPLE: I only wanted to make an observation that lumping adverse reactions as severe and life threatening is an apples and oranges classification. It's not what you usually do. You

lump serious, which has various definitions and life threatening. Severe alopecia is still not a life threatening -- so that's probably what leads to some of that confusion. It isn't the usual way we recommend doing it.

DR. SCHILSKY: I just had a couple more questions that came to mind during the discussion.

DR. AZAB: Sure.

DR. SCHILSKY: I just wanted to be clear. On the two randomized palliative studies, one of which I guess was actually closed prematurely.

DR. AZAB: Yes.

DR. SCHILSKY: Maybe you can explain why.

What was the statistical design of those studies? Were those studies designed to attempt to demonstrate superiority of PDT over YAG, or were they designed to demonstrate equivalence?

DR. AZAB: They were designed to demonstrate superiority in the YAG, actually. They had identical design, as I mentioned, and that was based, actually, from the protocol on one of the endpoints that that was not useful because it was an aggregate endpoint. That was a time to treatment failure. The design was to have a ratio of 1.5 of YAG over PDT, which means that PDT is about 50 percent

better than YAG.

The European study, or the Study P503 achieved the number of patients and the number of events that were required by the protocol.

You are correct, the other study, P17, was closed prematurely because of difficulty in enrollment. These studies were run between '89 and '93 and the Study P17 had one of the problems or causes of slow enrollment specified that all patients had to have recurrent disease and had to have prior therapy exhausted or prior therapies. Over the course of 14 months, there was only 71 patients included. At the time that was realized, we modified the criteria and Study P503 started, we allowed newly diagnosed cases if they were not operable to be included. Study 503 had no problems of enrollment and completed the enrollment and the number of events required for the analysis according to the protocol.

DR. SCHILSKY: I have one question about the superficial study. I believe Dr. Edell mentioned in his presentation that about 80 percent of the tumors were radiographically occult.

DR. AZAB: Yes.

DR. SCHILSKY: How were those patients diagnosed?

DR. AZAB: Yes. These patients were diagnosed usually because -- this patient population are a group we're presenting because of the indication that they are not eligible for surgery and radiotherapy. Most of them, as I said, 75 percent, had prior lung cancers and were followed up. So, these lesions were --

DR. SCHILSKY: Were these getting bronchoscopies all the time?

DR. AZAB: No. No, sputum cytology or bronchoscopy. These patients were either diagnosed by sputum cytology or by bronchoscopy because these patients had prior lung cancers and they were followed up. As we said, these are 100 patients in three institutions over ten years. It is not common.

DR. SCHILSKY: If I'm not mistaken, in the submission, at least some of the patients on those superficial studies actually had metastatic cancer, which I take it to be from a prior lung cancer. Is that correct?

DR. AZAB: No, no. Some of them had prior lung cancer of a higher stage, like the T2 or T3. None of them was metastatic --

DR. SCHILSKY: None of them had metastatic disease?

DR. AZAB: No, no. No, no.

CHAIRMAN DUTCHER: Dr. Raghavan?

DR. RAGHAVAN: Yes, I'd like to follow up on Dr. Margolin's question about the randomization process.

If I understood you correctly, you said that to ensure parity within each center, you had the full box technique in place. Did I understand that correctly?

DR. AZAB: The stratified by center, which means each center -- there were blocks by center. So, for each center, the randomization block of four, the block size of four -- that in each center when they reach four patients, they would have two PDT and two YAG.

DR. RAGHAVAN: Right.

DR. AZAB: But the block size was not known by the investigator, so they did not know that information. Of course, we don't provide it.

DR. RAGHAVAN: Right. But at least in practical terms, given that you did have a four block size, it's not unreasonable to assume that an investigator who was actively participating would know that, for example, on a random basis, he had drawn one PDT, one YAG, one PDT, and the fourth patient would

therefore have to be a YAG.

So that, what I'm getting at is what is the chance of bias here for an investigator to get the sense that as he already had two of one and one of the other, it was a pretty good statistical chance that the next one would be whatever was missing?

DR. AZAB: This is very difficult because as I said, we did not provide the block size. The balance of the patients could be at two, at four, at six, or at eight. And simply because the block size was four, so it was probably never a PDT, YAG, PDT, YAG. There was sometimes you could have two in sequence. So, they did not know the block size.

The randomization was central. They did not have the envelopes. That was done centrally. So, it is not possible -- I mean, it is very difficult to know.

CHAIRMAN DUTCHER: Dr. Ozols?

DR. OZOLS: Could you better define the contraindication you propose that it's contraindicated patients with a tumor eroding into a major blood vessel? I mean, many of these, obviously, had hemoptysis. How would you define specifically which patients you would not recommend this?

DR. AZAB: Yes, these patients, as I said,

as part -- many of them would have due to -- as the natural progression of the disease would have fatal massive hemoptysis. Actually, we have some data from the literature, from large -- of about 800 that has seven or eight percent natural incidence of fatal massive hemoptysis.

But to answer your questions, what we require is that the patients have the adequate staging usually, which is usually done for all these patients by CT scan. We use a contrasting fusion, rapid sequence imaging to identify if the tumor is very close to the vascular structure. If that's the case, then it should be contraindicated because there would be a higher risk of hemoptysis. But if you leave these patients -- actually, even those patients -- probably the natural -- any treatment -- it is not unique to PDT. Any effective treatment would have the same effect in terms of necrosis tumor. And if you leave the tumor to progress, it could have the same effect.

I don't know if Dr. Pass would like to add any further comment to that?

DR. PASS: Harvey Pass.

I think it's an excellent question. But my own thoughts on this is that these patients,

especially the early patients and the palliated patients are in some work-up at the time. So, I think that if a higher stage patient has an interbronchial tumor, that has to be worked up to see if alternative therapy, induction chemo-radiation therapy has to be done. They're going to get a CT scan.

So, despite the fact they have dyspnea from an interbronchial disease, that CT scan should alert the investigator as to whether it's going to be safe to relieve their dyspnea right now before they go on to, say, an induction chemo-radiation program. In the early stage disease, that may not be such a big problem. But I agree with you that the best standard techniques to rule out abutment or invasion of pulmonary veins, arteries or other structures should be performed.

DR. TEMPLE: Just a brief comment. We've usually accepted, I think, masked designs that used a constant block size. A lot of people now are varying the block size in sequence so that it's sort of a belt and suspenders. It's probably a little better, but that's a recent change.

CHAIRMAN DUTCHER: Dr. Krook?

DR. KROOK: A question because I suspect that somebody has some experience of doing this

therapy and then removing the lung to see what tumor remains. The question to Dr. Edell is, at Mayo, you kind of said that all people with superficial, or at least a large group, was getting the photo therapy. Has there been surgery done on some of these afterwards, to know what pathologically is present?

DR. AZAB: Dr. Edell, would you like to take this?

DR. EDELL: Okay.

DR. KROOK: I mean, here's a situation that's superficial, and then for some reason, surgery is done in addition, removal. Even the surgery in these superficial lesions must yield a fairly long survival cure. I'm just interested what pathologically it would look like, if you know.

DR. EDELL: In the study that I reported where we are treating surgical patients in a single arm, PDT first. If they have a complete response, they're followed out to two years every three months, and then yearly for a total of five years. We've had 43 percent of those avoid a thoracotomy at this time. Those that went on to thoracotomy, either because they did not have a complete response or they recurred, went on to surgical resection.

All of those patients are currently alive.

The follow-up is out over 62 months. Those patients that we republished had to have a follow-up of at least two years and we have no deaths in that group from cancer at this time.

DR. SWAIN: Do you have any comparable data with the YAG laser in the superficial group?

DR. AZAB: Dr. Edell?

DR. EDELL: We don't. I shouldn't say we don't. I mean, I have had patients who were non-surgical candidates with a little exophytic tumor who I felt were too bulky for a curative treatment with phototherapy. We would debulk with the YAG laser and then use phototherapy on the non-surgical protocol.

If you look in the literature, there are some investigators that have reported the use of YAG laser for superficial cancers. As long as you can tell the entire extent of these superficial cancers -- and they tend to be rather like crabgrass in your front yard. It's difficult to see where all the little carcinoma is going. You might be able to accomplish that in some very small lesions. The concern is that you don't end up treating the entire surface of the cancer. There aren't any studies that I know of in large groups of patients, using another modality other than phototherapy for these cancers.

There's some small series looking at interbronchial radiation therapy, but it doesn't come close to the numbers with phototherapy.

CHAIRMAN DUTCHER: Thank you very much.

I think we'll take a break at this point.

DR. SIMON: I have one more question.

CHAIRMAN DUTCHER: One more question. Okay, Dr. Simon.

DR. SIMON: Your assessment of objective response, did you say you have photographs of the diameter?

DR. AZAB: Oh, yes. All of these were evaluated. Actually, they were video settings. We've transcribed all -- because this is on video, all the endoscopy procedures. We just chose two examples of YAG and PDT that we provided to the Committee on the video. But we actually have for most of the patients, video settings of their responses and their --

DR. SIMON: Now, was there any review of that response assessment, other than by the physician who did the treatment?

DR. AZAB: No, there was no -- and sort of like an independent extramural review of these responses because it is very important to -- although you get the video for the confirmation, and it is

obvious for the tumors who have a complete response, for example. But for the assessment of the luminal diameter, it is best used during the endoscopy itself. It's very difficult to get a sense of confirmation of the luminal damage from just the video footage.

CHAIRMAN DUTCHER: Any other questions?

Okay, we'll take a break. We'll come back at 10 to 3:00 to hear the FDA presentation.

(Whereupon, off the record at 2:39 p.m., until 2:57 p.m.)

CHAIRMAN DUTCHER: Okay, we're going to continue with the FDA presentation.

Dr. Williams?

DR. WILLIAMS: Dr. Dutcher, Members of the Committee and guests, it's my pleasure to present to you the FDA analysis of the efficacy data of Photofrin for lung cancer, the efficacy supplement for lung cancer.

It has been an enjoyable process going through the data. We have a review team which I'd like to introduce to you. The medical, it's myself. And Robert Justice, the secondary review. Statistical, Tony Koutsoukos and Claire Gnecco. I left Richard Felton -- how could I ever do that? -- off the review. We don't usually have a device person

here, but Richard's from Center for Device review. He's been following Photofrin the eight years I've been following it, and I think he was following it before. Also, we have scientific investigations, Gus Turner, who will be looking at trials and the quality of the data. And then project manager is Paul Zimmerman.

Now, I never miss an opportunity to plug for good submissions of electronic data to the FDA, and this would be no exception. In this case, I guess I have an example. I really appreciate the good job that QLT did, both this time and in 1994, in getting good quality data to us. At least, I'd say good electronic data. Well, you know, I shouldn't confuse the quality of the data with the quality of the electronic submission. It's not necessarily the same thing.

The study reports and the protocols were in the word processor so you could cut and paste ad nauseam. The primary data, which basically in this case, the Photofrin data, was all submitted in an electronic form that was useful to me. In this case, it was in Access. Then there was good documentation of the data. You could understand where it came from, that it came from this blank in the case report form.

Then you could correlate back and forth.

We also had very good electronic mail communication. Some of the analyses you saw today were exchanges of E-mails this week. So, it's very helpful. And all of these things, I think we should be trying to arrange at the pre-NDA meeting. And I should say my presentation is somewhat more boring because of this because they presented some of my findings already.

The palliation indication, basically as you've seen, there were two studies. There was a European study which was basically finished, and a US study which was about one-third finished which was stopped due to poor accrual. They had identical designs, identical protocol. Both of them were randomized, open label, multi-center controlled trials with thermal ablation with the Nd:YAG, which I'll call YAG from now on, and PDT with Photofrin, which I'll refer to as PDT.

The primary endpoints of the protocol -- and we always start out an NDA review with review of the protocol -- basically was time to tumor recurrence. This wasn't practical because most of these tumors never went away. That was the primary endpoint. The secondary endpoint was sympto m

palliation which had problems because there was no perspective analysis plan which is key to evaluating symptom data. It's, as Dr. Simon has mentioned, subject to bias. You have investigators who know what they're giving, talking to patients. This type of data is sensitive to the quality of the data or the completeness of the data, and the data here was not complete. So, there's certainly problems with both primary endpoints.

Response was a secondary endpoint but there was problems with that too. Tumor measurements were part of the original response category, but in this case, they were not -- I think partly for technical reasons, they were not collected in many patients. I think rightly so, luminal diameter -- the 50 percent change in luminal diameter was considered as a reasonable response endpoint. There are problems with it though. For instance, is it clinically meaningful? Every 50 percent change in luminal diameter does not have the same clinical meaning. It changed from one millimeter to 1.5 millimeters. If that can even be measured, would be a 50 percent change. So, there are problems with that, but some of them are obviously clinically significant. There was not an analysis plan specified. When do you measure

it: at a week or at a month or anytime, et cetera?

So, these are the problems that when you come to analyze it, you have to make these decisions. They affect how you look at a p value because you've made a choice other than the one that's been specified. There was also, in the case of report form, there were data on the percent obstruction. So, instead of the number of millimeters, how much of the lumen was obstructed? That could have been chosen. So, these are the different problems one has to deal with with analyzing response.

Now, there are problems with the inherent nature of the treatments and with the protocol perhaps, in that the Photofrin was given at a different schedule as YAG and therefore, the data may be affected. If you look at Photofrin, it could be given every 30 days, may retreat in 30 days. Whereas YAG, it said -- of course, maybe have multiple laser sessions. Then the course ends if palliation is achieved or the investigator deems additional treatment would be futile. So, you've got a judgment here that seems to be coming a little earlier than on the Photofrin arm.

And here, it's rephrased in terms of removing patients from study seems to be somewhat

different. In Photofrin, if there's no evidence of palliation or objective response after two courses of Photofrin, then you remove the patient. But in YAG it said if further treatment is deemed futile, then you may remove the patient. Again, I think this implies if you don't have a success with your first treatment, then you would take them off in course one. Perhaps this summary is in for some differences in data collection.

There's certainly potential for bias in this study. Besides not being blinded, the treatment schedules you saw were different and therefore, you would have debridement that would happen and data can be collected at those points. So, there can be some variation in collection of data because the treatment was different. They defined the course differently. QLT has done an analysis, course one, month one. Well, if you define course differently in one than the other, then you have different data collected in the two arms.

And then there's if you get more patients dropping off study, there's a difference in data collection. If you have more patients off study in one arm such as, in this case, YAG, perhaps there's a less chance for response because you don't go on to

get that second chance. Perha ps there's less time to report adverse events. So, these may have bee n factors in some of what we see in the trials.

So, in general, I think statistica l comparisons between these arms are unreliable and if this is approved, wouldn't like to see them in th e labeling. The retrospective determination of th e primary response endpoint, that's something that was selected. And they've selected a time window. So , each of these affect my view toward you doing a statistical analysis. The actual analytical plan s were retrospective. Asymmetry that we've talked abou t in design, slight perhaps but some. And then this P1 7 was stopped prematurely and there was an interi m analysis some months before. So, again, these al l affect one's view toward p values in statistica l analyses.

The extent of follow-up was not tha t different. In the first 30 days, there were te n patients more who dropped out in the first 30 days on YAG. The median follow-up was the same. The poin t here is in terms of disposition of patients. You hav e about 35 to 40 percent in each arm who progressed, an d about 30 percent who died -- a few more who were not treated on the YAG arm. But 35 percent of th e

patients went off for some other reason and I believe many of these reasons are subject to bias. And this is an unblinded study. So, again, we've got missing data and the potential for bias.

So, I want to move on to -- and again, you've seen these analyses and you've also seen my analyses. This was QLT analysis of the month one time window for luminal response, or 50 percent change in lumen. Sixty-one percent versus 35 percent in the larger trial; 42 percent versus 19 percent in the smaller trial. And again, 32 percent of the patients versus 46 percent have no month one data. So, there are more patients in the YAG arm without month one data.

This is the analysis that I presented -- that the company presented that I did earlier, which was to look at day 18 and any point thereafter, not putting on an artificial time point, a time window. In this case, the Photofrin rate was 64 percent in PDT and 49 percent in YAG. Still superior, but not statistically significant if you're going to do analysis. In the other trial, 52 percent versus 22 percent. But by changing the time window, you can certainly change the degree to which the Photofrin is superior numerically to YAG.

I also did a few other analyses to get to the point of what's a clinically significant objective response. I looked at absolute changes of three millimeter, absolute of five millimeter, changes of percent obstruction rather than luminal diameter. I present those to you in my review. The concept from these is that Photofrin has a numerical advantage no matter which of those you do, but the difference is less marked. More of a lesser overall percentage, more of maybe 30 percent response rate with some of them. The greatest difference between Photofrin and YAG is seen in the one month time window. So, that particular analysis, I think because of asymmetry of data, seems to look a little better for Photofrin.

I think there are problems with the other endpoints, time to treatment failure and time to local progression. I said that their endpoints -- aggregate endpoints of fuzzy elements. Things like, you know, going off study -- the patient went off study because they wanted to or because they wanted to get other treatment. Those sort of things that we have difficulty saying that the bias is not involved in.

You've seen these data on the symptom improvement, 30 percent versus 17 percent for dyspnea. And for cough and hemoptysis, not quite as much but

still numerically superior findings for sympto m improvement. But again, you look at the missing data , 26, 28 percent versus 41 to 44 percent -- a good deal of this just could be because the patient isn' t reporting improvement. So, I think we can't make any strict statistical comparisons between arms.

So, with the symptom data, there's n o prospective plan. There's missing data -- a larg e amount of missing data and it seems to be asymmetric. The month one cutoff favored P hotofrin. For example, I looked at the two analyses doing month one versu s any time, and by doing the month one, you exclud e eight improvements on YAG versus two on Photofrin . So, there seems to be, certainly, some bias in th e time at which data was recorded.

The applicant has already defined thei r clinically important benefit definition, and the y found 36 patients on Photofrin and 23 on YAG that had clinically significant improvement, or clinicall y important benefit. I looked at the graphica l summaries of these patients which, I think you hav e examples in your background briefing package whic h would put the objective respon se and the toxicity and the subjective tumor -- the symptom data. And jus t sort of a gut reaction, does this look real or i s

this, you know, an accident of the numbers? Looking through them, I agree that just my gut feeling is that 33 of them seem to be genuine because several of them had more than one category. So, they would have a tumor response and then they would have a symptom benefit. But again, that's not hard. It's just a quality control of categories that they've submitted.

Toxicity -- I think all of these have been discussed before. There's more in photosensitivity, psychiatric, dyspnea, bronchitis. Now, hemoptysis is not statistically significant, but you keep seeing it being a little more on Photofrin throughout the trials.

More serious problems, fatal massive hemoptysis. If you look, again, it's not statistically more. There are 10 in Photofrin and six in YAG. But what is very clear is that the prognostic factor for this is prior radiation therapy, 24 percent versus 14 percent, versus two percent and zero percent. Again, this may just be a marker for patients who have had disease longer. I don't know, but it's very clear that this is a group of patients who have a higher risk of hemoptysis, both on Photofrin and YAG.

Looking at adverse reactions, again, we

won't call them life threatening, but very severe. Severe was actually a little higher in YAG and very severe quite a bit more on Photofrin. Many of these were pulmonary, dyspnea -- put together dyspnea, hemoptysis, coughing. I'm not sure coughing was in there, but most of them were pulmonary. However, there was not an increase in deaths within 30 days, which I think we'd be looking carefully at. Median survival, they're not powered to detect that. But for what it's worth, it was not different.

So, to summarize my findings, that over 50 percent of the patients in each study had luminal response at some point after day 18. Thirty-two percent had this category identified as clinically important benefit, which is an aggregate of durable response and larger changes in symptom grade. But I would say that the data all shows Photofrin to have numerically superior values. I would frown on any statistical comparisons.

In terms of safety findings, there was more photosensitivity, dyspnea, bronchitis and psychiatric adverse events. This one I'm not sure about. It was only seen in one trial. I don't understand it. It's anxiety and things like that. A non-significant increase in hemoptysis and fatal

massive hemoptysis.

So, those are my findings. I'd be very glad to get your input on this because I think there's efficacy. There is evidence of patient benefit and there's evidence of toxicity. I think it's a value judgment which ODAC would have a very strong hand in the making.

The second indication was for superficial lung cancer. These, again, were single arm studies. As you get into the study reports, you realize that they're all not really prospectively following a protocol. Study P506 actually is compassionate use data that was retrospectively gathered and they were more treated with, I think -- they may have been treated with a protocol but there was no one specific protocol. Fourteen of the patients in this study -- 14 out of 32 -- were treated with a protocol, a different protocol that retrospectively gathered together because they were in this group of patients. And then this French study, they were all put on protocol. Actually, the best quality of data may have come from this study, the German study. Certainly, the very high adverse reaction rate I think was due to the meticulous collection of data.

I think the first big question is was

surgery and radiation contraindicated in this group of indication patients? Because we are assuming that radiation therapy and surgery are standard treatments and that there's a group of patients out there that can't get radiation and surgery. We are viewing some of those patients. The way I broke it down was to look through the listings. Seventeen of them either had multi-focal disease or had previous radiation therapy. In discussing with radiation therapists, these are pretty good exclusions for radiation therapy. In the other seven, their pulmonary function rate ranged from FEV_1 to .6 to one liter.

So, I would say that if there is a group, this is the group. I believe there are surgeons that are doing very selective surgery that might consider they could operate on some of these patients. But when you get down to multiple tumors and patients with bad lung function, I feel like this group is as close as you could get and I think your input is valuable here also. There were analyses done recently -- I don't believe that they're any thing that I have given you -- that show that the efficacy we've discussed, but the safety also was similar to that in the all patients' analysis. So, safety and efficacy were similar in this group to the all patients' analysis.

But then the question is, what are the results? The methodology that I used in my review, the main work I did really in this review was to review individual case records in various ways to establish what the last biopsy date was. What I found was that in the time to recurrence listings, there were very large gaps between the last biopsy date and the date of recurrence. So, there were patients that had a last biopsy on day seven and maybe they dropped out on day 1,000, and they were being called duration of 1,000. Or perhaps they recurred on 1,000, but they were having a duration of 1,000, which would have a dramatic effect on your time to recurrence curves. The frequency of the biopsies obviously were nothing like what the protocol specified, which was about every three months early-on. And that there were many CR1 biopsies that only had very early biopsies. Yet this was their evidence of complete response.

So, what I presented here, I made up my own CR1 category, which is a three month CR1 which is really quite standard, I think. If you look at bladder cancer, superficial bladder cancer, et cetera, they all require at least a three month follow-up before you declare CR. QLT's findings were a 79 percent response rate in all patients and 92 percent

in indication. And then applying the three month standard, mainly due to lack of biopsy -- not that they recurred early, but just the fact that they didn't have a biopsy after that early biopsy to demonstrate that they were in complete response, it dropped to 47 percent and 62 percent. So, the overall groups dropped.

I thought it was important, and I'm having problems deciding about the carcinoma in situ group. What is appropriate for that group versus what is appropriate for the T1 group? And again, I think Committee discussion of this would be important. The T1 group and the Tis group had about -- well, let's see, in the applicant's response, it was 82 percent versus 96 percent. In the FDA analysis, they were both about 50 percent. The T1 was 50 percent and the Tis was 50 percent. The question is, what does this mean? What is the natural history of T1 versus the alternate treatments? What's the natural history of Tis versus alternate treatments? I think it's a very difficult question, but I think it's useful to divide these out. I would assume that T1 patients recur sooner clinically then Tis patients and would probably be justified with getting a treatment with more toxicity.

So, here are other findings in the T 1 patients. I mentioned the 51 percent three mont h response. I also looked through the listing an d looked at one year CR1 biopsies proven complet e response. Thirty-one percent had it documented at at least a year. And as you look through the listings, I think, of the most recent re view update I sent you, the listings of patients whose biopsies are ou t farthe r or who maybe died without evidence of tumo r sometime out. There are people who go out farther . But these are the hard data for CRs extending to thes e times.

Median diseased specific survi val was 5.7 years. I think this is a valid data point in th e original application, survival 3.5 years. Advers e events, severe in six percent, life threatening or we should say very severe -- I'm not sure what they are anymor e, but they are five percent. Some of thes e really were life threatening. That's very clear. In this case, I think these were.

One particular study had a very hig h incide nce of adverse events, of the German study . Part of it may be that they we re collecting predicted events , but there was a 33 percent incidence o f stricture. They had more severe and very sever e

events also. So, I have some suspicion that the adverse event rate is higher than is reported in the other studies. I think there's good evidence that they didn't do biopsies very rigorously, and I think they might not have collected adverse event data as rigorously.

I think there's one fatal massive hemoptysis death from Photofrin. It happened 20 days after a procedure. Originally, this patient was said to have a CR with one of the early biopsies, so I can't imagine how they could have fatal massive hemoptysis from anything but the treatment in the very early cancers.

So, I think the two questions here, in view of the natural history of superficial tumors, do the response data represent clinical benefit for this group or for a major subgroup? So, do you see evidence of clinical benefit? Then the second question is, were the surgery and radiotherapy indeed contraindicated in the indication patients? I think the construct we're using, we need to have your opinion on both of these. We'll certainly be very interested to hear your discussion.

Thank you.

CHAIRMAN DUTCHER: Thank you.

Do we have questions for Dr. Williams?

DR. WALKES: You said that the one death from fatal massive hemoptysis was, you thought, because of the PDT. Was that one of the patients that had had prior XRT?

DR. WILLIAMS: That's a good question. If they had had brachytherapy at that site?

Oh, okay, yes. That's okay. And so, four months before, they did have brachytherapy. So, that would temper you a bit, I guess. But still, 20 days after you get treatment is --

DR. WALKES: So, why is it that you get FMH more often when they've had prior XRT?

DR. WILLIAMS: I don't know why for either YAG or PDT that you get a higher incidence of fatal massive hemoptysis. It's clearly there. I think that a complicating factor is that most of these patients are also going to be later in their tumor course. So, whether if they're later in their tumor course -- and I don't know -- I haven't seen a multivariate analysis or anything to see if you can separate it. I doubt that we have enough data to do that.

I wonder if there are any comments from the company?

DR. AZAB: Can I have slide 192, please?

Can I have the previous slide, please? Yes. The next slide? Okay, I'm sorry. The next slide, next one. This is some of the reported incidence on the literature in treated with different treatments with the brachytherapy ag or external beam. As I said, in the summary, they were between four and 32 percent. Actually, interesting, very recent '96, '95, a very large series of patients treated reported incidence of eight percent to 21 percent.

Next slide, please?

And these are actually from all the series, the compilation of the risk factors for fatal massive hemoptysis where the squamous cell carcinoma, in particular. The majority of the patients in these trials are squamous cell carcinoma in the trials we presented. Those have more tendency to have cavitation. In all those of those series, they reported prior high dose radiotherapy as indeed a risk factor, and also the location of the tumor. So, I think, I mean, it's just that it is probably patients who had a more advanced disease or probably the prior high-dose radiotherapy could have some form of effect on that, but these instances in the various series are usually what is reported in the range.

CHAIRMAN DUTCHER: Doctor Schilsky.

DR. SCHILSKY: Grant, I had a couple of questions. One may seem a little bit trivial, but I'm real curious to know your thoughts on these psychiatries AEs. No one has really discussed that, and it sort of hangs out there. It's not clear to me that there is a logical mechanism, you know, for those, unless it's just some actual toxicologic effect of the Photofrin. Do you think those are real? I mean, do you think they are treatment related AEs, or are they just events that are happening in a sick population of patients?

DR. WILLIAMS: I didn't really look too carefully at the timing of those. They were only in one study. Again, I think maybe that was the German study, which collected probably more rigorous data on adverse events. So, I really don't know.

I think that's the kind of thing we need to build into these sort of protocols when you are trying to compare quality of life, you need to build in time points where they are likely to be suffering from whatever that treatment is. So, I really can't say.

DR. SCHILSKY: I guess my other question, it seems to me that in the superficial studies, you know, that the critical factor we are going to have to

consider, I guess, is based on the time to recurrence. There's really not that much in the way of response data and probably not that much in the way of symptom control for these very early stage tumors. And so, I wonder if you could give us your thoughts again on the issues that we need to think about with respect to how recurrence was documented. Was recurrence always documented based upon repeat biopsy, or in some cases was there actual clinical evidence of, you know, radiographically documented recurrence?

DR. WILLIAMS: I think it's a very difficult issue because the patients have multiple tumors. They'll have a superficial tumor which you are doing a superficial treatment, you don't know if it's growing deep, you don't know if a CT scan has been done, and then they have metastatic tumor, you don't really know if it's from there or the other.

The disease specific survival analysis that the applicant did is valid. Every one of those had cancer of some sort, but whether it was from this cancer I don't know.

Now, you know, in the table that I tried to prepare, what I did was to censor everybody at their last biopsy. People that recurred I said they failed at some time point afterwards, but I think it's

an unrecoverable lack of data. We can never know the difference between a clinical recurrence and when you would have known it if you had adequate follow-up, and these diseases we don't really know the natural history of, you know, both CIS and microinvasive, so, you know.

DR. SCHILSKY: Well, it's still quite remarkable to me that this group of patients, with really poor pulmonary function in general, many of whom had prior history of other lung cancers, you know, had a median survival overall of three and a half years. I mean, are you impressed by that figure as well?

DR. WILLIAMS: Well, I don't think we have adequate historical controls. Almost all the historical controlled series have some more advanced tumors in them, and this is mostly microinvasive disease. So, I think we'd have a difficult time looking at survival data in a comparative sense with historical.

CHAIRMAN DUTCHER: Doctor Justice.

DR. JUSTICE: I just have a comment on the question about the psychiatric AEs. I think it's not unreasonable to expect there would be a higher incidence with Photofrin, because you are -- the

patient would be worried about photosensitivity and be sort of stuck in the house for 30 days, so it wouldn't surprise me.

CHAIRMAN DUTCHER: Doctor Temple.

DR. TEMPLE: Grant, you described the analysis you did as censoring patients at the time of the last biopsy. I hesitate to do this with a lot of knowledgeable statisticians around, but I think actually what you did is not censor them, but you attributed them as not having complete response and maintained the same denominator that they started out with, which is not what I understand censoring to be. You did what you could call --

DR. WILLIAMS: Well, no --

DR. TEMPLE: -- worst case analysis.

DR. WILLIAMS: -- what you are talking about is for this. Now, I never really did a time to event curve, but I did prepare data so that could be done. So, I would have censored time -- those are times when I would have censored it in a time to event analysis, and I think -- you did the analysis, basically, why don't you go ahead and present that. I don't know if you wanted to see it or not.

DR. TEMPLE: But, my understanding is that you did what would be called a somewhat more

conservative analysis, you just said if there's no biopsy you can't count them anymore, and you didn't censor them.

DR. WILLIAMS: Yes, for response.

DR. TEMPLE: For response.

DR. WILLIAMS: For response rate, yes, three month response, one year response, yes, that's what I did. For time to timber progression, instead of censoring the people that failed, I added 90 days and said, well, that's when you had your biopsy and we've known it. That's also very conservative.

DR. SWAIN: Grant, for the indication patients for the superficial group there were 24, and I think about ten of those had TIS alone. Was the only indication for any intervention at all just the diagnosis of TIS, I mean, since that's, I guess, somewhat controversial now, and some people may actually just follow these patients and not intervene at all.

DR. WILLIAMS: That's what their indication for treatment was. I don't know what the indication for treatment is now.

I think QLT would like to present a natural history of superficial disease. I think it would be helpful, it relates to this NCI graph.

DR. AZAB: In terms of just for the psychiatric events, because I know Doctor Schilsky asked before. Perhaps, I made the comment in the presentation, they are all transient mild to moderate anxiety or insomnia, usually reported on one day before or after the procedure and then disappear. So, that's it.

DR. EDELL: I think the -- well, this just shows some information that was taken from the major screening studies that took stage one cancers that had some TIS, but these were stage one cancers, and shows the difference between those that had surgery and those that didn't, but those were a lot of peripheral nodules as well, so, in those patients that have stage one cancer.

But, the issue that you raise is one of carcinoma in situ, and in our institution I think now we consider that cancer, and there are molecular biological studies to show, at least from what I've heard reported in Dublin at the International Association of Lung Cancer meeting, to show that there are irreversible genetic changes that are occurring in in situ lesions.

And, I think that if nothing else, this kind of therapy offers an opportunity to start to

catch these at a very early stage, and I think the carcinogenesis for squamous cell carcinoma is becoming much better defined, similar to what we've seen maybe in colon polyps and colon cancers, and that this lesion is a very important lesion, at least in our feeling, for eradicating a process that's going on to go on to an invasive cancer.

Harvey, do you have a comment?

DR. PASS: Yes. I think this is a very timely question, and I think it's a very timely issue, because the data that was just talked about at the ISLC had a tremendous amount of input on this very question.

And, most recently, there are changes in oncogenies being fit, as well as tolomerase activity in carcinoma in situ that start at carcinoma in situ, as well as microsatellite instability.

I think the important thing to remember here, whether this is to be treated or not, is that there is a parallel with cervical cancer, number one, and, number two, that carcinoma in situ in the lung cancer situation is no longer looked at as just some sort of benign lesion, and, indeed, screening programs are advocating treating carcinoma in situ.

Also, for this population of patients, for

this indication, remember that the treatment of this carcinoma in situ is in patients who have no other options, meaning that they could not get surgery or radiotherapy.

CHAIRMAN DUTCHER: Doctor Raghavan.

DR. RAGHAVAN: I'm still, I guess having move to the West I've slowed down, I'm still having trouble understanding this latter group of patients that Grant -- that Doctor Williams has struggled with. Can you explain, can somebody explain to me, the criteria for entry into this group, did you have central pathological review? How did you differentiate dysplasia versus carcinoma in situ? I mean, what are actually treating here, because this is what I'm wrestling with. I've had less trouble with the first half of the presentation, but I actually don't know what you've treated. I can see the classifications of TIS T1 and T2, from studies done overseas. The indications to me are very confusing, the indications for not operating are not clear, but my fundamental problem is a natural history question. I understand the data presented from Mayo and the summary of the results of what happens to proven carcinoma in situ from screening studies that are well controlled, I'm having difficulty saying that this is

a well-controlled set of patients.

So, I don't know what you've treated, so could somebody enlighten me, what got you into the category of carcinoma in situ? What were the changes? Who called them? How reproducible were they? Was there anybody who was labeled with carcinoma in situ, or were these reviewed by an expert tumor pathologist?

DR. WILLIAMS: Well, I'll start off and then definitely hand off.

Certainly, there were data presented on, say, tumor area, this many millimeters by that many millimeters, and most of the protocols -- the intent of the prospective protocols and the retrospective selection was that they be radiological occult, which does tie it to a group in the literature. But, it also had CIS, which most of the literature is, say, T1s are radiologically occults, so this is a mixture, basically, that you had cancer and radiologically occult, I think.

But, certainly regarding the quality control of the biopsies, et cetera, I don't believe that was done, and I'll let QLT -- it's not.

DR. TEMPLE: So, that means it was the local diagnosis.

DR. WILLIAMS: Right.

DR. TEMPLE: You just took the ir word for it.

DR. WILLIAMS: Local diagnosis, and what I reviewed were words, I didn't have biopsy reports, words that said carcinoma in situ.

DR. TEMPLE: But, presumably, if that wer e impo rtant, one could at least haul back those pat h reports and look at them.

DR. WILLIAMS: I think that part of th e audit will be our auditors' ability to verif y diagnoses.

DR. TEMPLE: I actually don't think that getting back the path reports is helpful, I think it' s gett ing back the slides, because we've had this a t this committee before, as soon as you intrude into th e area of carcinoma in situ, someone cited the analogy of cervical cancer, but that's now totally different. I mean, there's such rigorous quality control, eve n out in the community, whereas, the handle of dysplasi a versus TIS in pulmonary pathology is an evolvin g field, and that's the problem with historica l controls. What used to be dysplasia might now still be dysplasia, or it might be TIS, or it might b e nothing.

And so, when we talk in terms of th e

impact of this treatment on that entity it becomes hard for me to attribute an impact when I don't know what the entity was to begin with.

DR. RAGHAVAN: I didn't actually mention this in my review, but one of my concerns -- I mean, in my presentation, but one of my concerns with this is the idea of reproducibility of diagnosis, you know, you have a patient at baseline that had a small CIS, did they or didn't they get a biopsy or cytology, and they didn't do it frequently, what is the one time chance that you are going to miss it, those sort of things.

So, I certainly feel like there wasn't a lot of the rigorous type of follow-up that I would want to see to document that follow-up was at CR, a one-time biopsy in many patients.

DR. TEMPLE: If that were a critical point, wouldn't it be possible to get the slides and have them looked at by an expert group?

DR. WILLIAMS: They could try, they said.

CHAIRMAN DUTCHER: Doctor Johnson?

DR. JOHNSON: Well, I wanted to sort of continue to beat this horse a little bit about the TIS. You've subset a subset into an even smaller subset when you take a group of patients that have

carcinoma in situ.

The fact of the matter is, many good thoracic oncologists don't treat carcinoma in situ, even when patients had the ability to be resected, and we've already heard from your consultant, the radiation oncologist, that the dose for treating carcinoma in situ is unknown. So, we are extrapolating treatment to a group of patients who don't necessarily get treated with two modalities, that they are not eligible for anyway.

In some instances, patients may be followed, that may be the total sum of their management. They get nothing done except for periodic bronchoscopy.

So, again, I think Derek's point is a very good one, Doctor Raghavan's point is a very good one, we are trying to struggle with these data to try to come up with, what have we done for the patient of great benefit.

Now, if you tell me that you managed to make a small area TIS go away, all the molecular genetics aside, the reality is that the entire aero-bronchial system is at risk for recurrence, and I'm not really sure that we -- I mean, we've shown even when you cut out those areas, you've not necessarily

altered the natural history of that patient. You may not have changed that patient's life one iota. So, I'm not sure that -- I mean, even surgery may not benefit this group of patients, is what I'm trying to say, if they were able to be operated upon. So, you taken another group that we can operate upon, we've applied another modality that we know even less about.

So, I think it's a very tough group of people for us to analyze.

CHAIRMAN DUTCHER: Doctor Temple.

DR. TEMPLE: I guess I want to ask Doctor Johnson, the remedy for that, I presume, is to take people with this diagnosis and no other lesions and randomize them to watchful waiting versus some modality or other, is that what you are saying?

DR. JOHNSON: Yes, I think that it's a good attempt to get some sense of the value of this approach, but now I think you have convinced me, at least, that you have a modality that makes TIS disappear in some instances, and now you can test it.

DR. TEMPLE: And, there are at least some institutions that would be comfortable doing that.

DR. JOHNSON: Sure, I think the Mayo Clinic would probably be comfortable testing that, maybe not. Wayne State probably would. And, I

suspect an institution like my own would be intereste d in doing that.

CHAIRMAN DUTCHER: Any other questions fo r Doctor Williams, comments?

Thank you very much.

So, we should go -- any other comment s from any members of the committee before we talk abou t the questions?

Doctor Ozols.

DR. OZOLS: I guess if you raise tha t issue that randomized trials s hould or could be done, in which patients with carcinoma in situ ar e random ized to treatment or to no treatment, I'm no t sure what we'd be really addressing in evaluating a possible "treatment." If you are telling us tha t there is no treatment or no es tablished need to treat these patients, or they are cl early not proven yet, I guess I'm perplexed at why we would prove this as an indication.

CHAIRMAN DUTCHER: I think that was th e question. Well, let's go on to the questions that FD A has asked us to address and discuss, and the first on e is, in obstructing lung cancer, in the obstructio n indications, two prospective r andomized trials, P-503 with 141 patients, and P-17 with 70 patients, compare d

photodynamic therapy with Photofrin to YAG laser therapy in patients with obstructing non-small cell lung cancer. The applicant's analysis of month one response rate, the rate of increasing the diameter of the obstructive lumen by at least 50 percent from baseline on days 18 to 45 for Photofrin was 42 percent in trial P-503 and 61 percent in trial P-17.

In each trial, the numerical response rate was higher on the PDTR than on the YAG arm. This analysis and the FDA analysis response, which included all data on or after day 18 are summarized in the table that you can see in this next page. Maybe I don't need to read all of this.

We'll go on to the next page. Okay. Then there's a discussion of the above table, describing symptoms, okay. Applicant found that in 36 of the 102 patients randomized to PDT, and also in 23 of 109 patients randomized to YAG, such clinical benefit could be demonstrated.

Do these two trials serve as adequate and well-controlled trials demonstrating the efficacy of Photofrin for treatment of patients with partially or completely endobronchial non-small cell lung cancer?

Who would like to -- Kim, Doctor Margolin?

DR. MARGOLIN: I wouldn't like to, I would

just like to point out, I don' t know how important it is, but I really think, as part of our origina l discussion at the top of this page that it's a third to a fifth of the patients' doctors reported them to have an improvement in dyspnea cough and/o r hemoptysis.

CHAIRMAN DUTCHER: You mean, you want to modify the statement?

DR. MARGOLIN: Well, I don't k now that we need to modify the statement as it is written, bu t just point out that that was part of our origina l discus sion, and that may be part of this subjectiv e analysis of the quality of life issues here.

CHAIRMAN DUTCHER: Okay, clarification.

Does anyone want to initiate a discussion of an answer to this question? Doctor Schilsky?

DR. SCHILSKY: Well, I'll start off. I don't know that I'm prepared to answer the question, but I'll tell you why I'm having so much difficulty.

It seems fairly clear that there were man y proble ms with the way both of the randomized trial s were conducted. In fact, one of them wasn't eve n completed. And, in the one that was completed there are many, many problems with the data, there ar e problems with the initial definitions of endpoints ,

there are problems with missing data, to the point that, at least the FDA concluded that, the statistical analysis was unreliable, which I tend to agree with.

So, in my mind, if the statistical analysis is unreliable, then in a sense there's no point in trying to compare the two arms of the studies, and I think that what we would be left with then would be to say, okay, well, let's just look at these as single-arm studies. What if these were just a bunch of single-arm, phase two studies that were presented to us, and so we have, say, two studies of Photofrin PDT, and we put that in the universe of knowledge with respect to experience with YAG therapy, including that, you know, which was presented today.

So, if you view it that way I guess, then I come down to, well, if you consider these to be single-arm studies, then do they present sufficient evidence of clinical benefit for the patients that would justify recommending approval.

And so, first I would have to say that in thinking through it in that way, I then immediately would discount the response data, because the response data, by itself, doesn't convey any information to me about whether the patients benefitted or not. So then, we are left with the symptom data.

There are questions about the reliability of the symptom data, with respect to how the information was obtained, whether it was reproducible or not, whether it's even complete or not.

And, at best it would seem that 30 to 50 percent of the patients have some symptomatic improvement for some period of time. So, I guess I would just like to initiate the discussion maybe by seeing if others on the committee would accept this construct of how to look at the data, because if not then we can talk about other things.

But, I think one of the things we are going to have to decide is, if this way of thinking about it is reasonable, you know, is the data sufficient to allow us to make a determination as to whether the patients actually obtain clinical benefit from the therapy.

Maybe I'll stop at that point.

CHAIRMAN DUTCHER: Doctor Raghavan.

DR. RAGHAVAN: I think that Doctor Schilsky has summarized very eloquently the difficulty that we are all wrestling with. Really, what it comes down to is the tension between the, as he termed it, the universe of knowledge and some really pretty poor clinical trial data that have been presented.

And, the difficulty is to set the balance between process and logic. As a clinician who has collaborated with people who have used photodynamic therapy in this clinical context, I have the personal experience that hasn't been cited here of having seen patients who were clearly not accessible to YAG laser therapy for technical physical constraint reasons, who have had maximum dose radiotherapy, who have had chemotherapy, who come within the purview of this set of randomized trials, and I've seen clinical benefit in this situation.

So, on the one hand, logic would tell me that this is a technology that has a place and where some patients will benefit, and I personally haven't seen a lot of toxicity, although my experience has been indirect and limited.

On the other hand, process is important in the sense that it would be a very poor precedent to set that would allow the FDA to approve material presented of poor quality data, and some of the data, as presented, is of poor quality. There are a lot of unanswered questions. There is lot of imprecision for many of the cytotoxic moieties that we look at. On the strength of this information with an absolutely brand new technique, we would be obligated to turn it

down.

I think as this is currently s till in the discussion phase, I think that my advice to the FDA i s that for this first indication the balance o f probabilities would favor approving it, but with a very clear message that this shouldn't be seen as a precedent in terms of the quality of the data that ar e being submitted today.

CHAIRMAN DUTCHER: Doctor Johnson?

DR. JOHNSON: I was, I think, agreein g with Doctor Raghavan all the way up to the end, s o I'll preface my comments by saying, I thin k intuitively those of us who deal with lung cance r patients believe this approach should work, and , therefore, are looking for justification for approvin g it for that purpose.

To directly address the questi on asked, I had these thoughts, both phase three studies wer e designed to demonstrate, not a comparability between the two, but actually a superiority of the PD T approach, which I think is an admirable thing to d o and, frankly, a lot more pract ical thing to do, since comparability studies are ofte n difficult and require huge numbers of patients.

In that sense, both studies fa iled. They

were negative studies. So, the answer to the question, in the strictest sense is, do these studies serve as adequate and well-controlled trials demonstrating the efficacy of Photofrin, and the answer is no.

But, I like Doctor Schilsky and Doctor Raghavan, I'm a clinician and feel intuitively this ought to work, and so we are left with something of a dilemma, and that is, you know, what should we do to, perhaps, approve this product for this indication.

And so, I'd, like Doctor Schilsky, turn to the concept of clinical benefit, and that, to me, means if the patient perceives that he or she has been benefitted by the therapy, and in this case that means symptom control, then is the basis of my several questions related to symptom assessment.

And, I concur with Doctor Simon that the method by which symptoms were assessed in this study are subject to huge bias in my view, and, therefore, I think these data are, at best, problematic, and I can't bring myself to suggest that I am persuaded by the data that have been presented that the patient has clearly benefitted, you know, from a symptomatic point of view.

But, with regard to this first question,

I think my view is the answer is no.

CHAIRMAN DUTCHER: Others? Doctor Margolin?

DR. MARGOLIN: I have a comment, but it's not directly responsive to what Doctor Johnson was saying, it's just in general. I think I recall correctly from the discussion we had several years ago about this approach for obstructing esophageal lesions that one potential option for approval would be consideration of this as an alternative to YAG in selected patients.

The problem is that we don't have patient characteristics from this data base that would suggest those who might be most appropriate for YAG and those who might be more appropriate for the photodynamic therapy. So, it's more of a generic suggestion, but I think, perhaps, it should be out for discussion.

DR. SWAIN: Just one comment, going along with what Doctor Johnson said. I guess I'm more persuaded by the lack of clinical benefit that I've really seen here with more dyspnea and more bronchitis, psychiatric symptoms, more bronchoscopies in the patients, and really having a hard time believing or looking at the data in my own mind, showing that the benefit is greater than all these

risks.

CHAIRMAN DUTCHER: Let me ask a question of Doctor Johnson and Doctor Schilsky, and maybe Doctor Raghavan. If a patient with an obstructing lesion appears, and an intraluminal procedure is going to be done, is there a need for another option than laser, YAG laser?

DR. RAGHAVAN: Well, since the other two haven't said anything, I think the answer is yes. That's the basis of my comment.

I don't think it's a big group, but I think, as I mentioned, that there is a subset of patients that pulmonologists and thoracic surgeons will see where technically it is not feasible to get the structure of the YAG laser in place to remount the obstructing lesion, and you can actually thread down a core into a physically obstructed lesion where you just sometimes can't get the YAG laser. A good example will be at a take-off point for a smaller airway, where you have the technical concern that where the endobronchial passage takes a right-hand turn, your instrument will continue to go through the wall of the vessel creating a bronchopleural or some other type of fistula.

So, I think the answer to your question

is, there are indications, but all of this data that we've heard today doesn't addr ess that question. So, that's where I came back to my point of saying that's it's process versus logic. I think there is a subset of patients who will definitely, in my mind, benefit from having the availability of this technology, but it's not a very big number.

CHAIRMAN DUTCHER: How would you prov e that? If these data don't prove that, and we decide that there's not sufficient da ta for this indication, how can one prove that you have a new technology that , in fact, can be beneficial for subsets of patients?

DR. RAGHAVAN: I think it's a ver y difficult study to design, and it would take tim e because it's not a very large number of patients . And, my guess is that if we made the technolog y available for such a small subset, it's the sort o f thing where I suspect a company would take a look at it and say, the profit margin for such a small group of patients doesn't require us to invest the money to answer the question.

The only way I could think of doing i t would be to set up a design where you identified a series of experts who would prospectively identif y patients with obstructing lesions who were no t

eligible for radiation, who were not eligible for surgery or chemotherapy, and for whom the YAG laser did not provide adequate technology. And, as I said, this would be a small group, you couldn't do it in a comparative arm, and then, ultimately, it would come back to a committee like this, which would find post-hoc flaws with the study design.

So, my guess is that we've got to bite the bullet today. I don't think -- I mean, I think the problem is when these studies were designed initially they were flawed in their design, there were trucks that you could drive through the holes in the way the data was constructed, and so I guess it creates a real difficulty. I don't just feel intuitively that this is a potentially useful technology, because I've seen cases where thoracic surgeons and pulmonologists have managed patients that I've referred to them with this technology, explaining to me, and with no connection with this committee, that the YAG laser wouldn't do the job.

Again, I come back to the point, this is not a very big group, and then the question is, do you give an approval then understanding that, depending on the nature of the indication, it could be an abused approval.

We come back to the fact that this technology is used for esophageal lesions, as I understand it, it's hard to artificially describe a difference between the entities, but I think Doctor Johnson's point is admirable, and I think he's right. I mean, if you do it just on the data that are sitting in these books, it's very hard to go with it, and I'm deviating from my normal practice of just going on the data, and maybe that's an incorrect thing to do, but I am struggling with it.

Doctor Ozols looks like he wants to buy in.

CHAIRMAN DUTCHER: Doctor Ozols.

DR. OZOLS: But, the point, I guess, is that we should approve things on a basis of scientific well-controlled trials, and I think we don't have that.

On the other hand, you suggest there is a benefit, and I tend to agree with you, but I don't think we are harming patients by not approving it at this point, because, in fact, a drug is available, and I think people in the community are doing it. So, maybe we can't define the specific characteristics of the patients who are getting this, but I think they'll continue to get it, those that you described, Derek,

that, you know, may benefit from this, they'll probably continue to get it whether or not we approve this or not at this point.

But, I think to say that we can't define a group of patients and get a trial that shows it, I think is not the right message, I think if this stuff works we should encourage the sponsor to do the trial to show, in a very discreet population, that there is some benefit.

CHAIRMAN DUTCHER: Doctor Temple.

DR. TEMPLE: I want to be sure I understand what everybody thinks is wrong. These were randomized trials, that doesn't happen all the time on the things that come before this committee. They did not blind the observation of endpoints that are subjective. They didn't even have a blinded observer do them. We always advise people to do that, but our advice is rarely taken, and that would be an improvement.

It seems to me there's at least some internal evidence, however, that people were paying attention and were not necessarily biased. There's a difference between the one week and the one month observation. If you think people are biased in reading things according to how the therapy they gave

worked out, it would be hard to explain why at one week symptoms are all sort of even, and at one month they mostly favor, at least moderately strongly, the Photofrin therapy, so I just throw that out to think about.

I guess I have to note that what Doctor Raghavan described as obvious clinical benefit is just the same thing that these people reported, and I guess one believes it when one observes it, and is skeptical when one doesn't. I mean, we share the same thing, these are, you know, dyspnea and all these matters are highly subjective, they are obviously amenable to all kinds of influence, but there is that one point within the study that suggests that they may have been reporting something more than completely randomly.

I guess the other thing I'd be interested in comments on is, when you shoot for superiority and don't quite get it, but you are quite sure that you could measure response rates using the historical control methodology or whatever, how much does that matter? This doesn't have to be superior to YAG laser, you just have to believe it has a response, and then the question is, have you shown that that does any good?

Well, the way you show that it does any

good is all the symptomatic improvement, and we need to be clear, if what the committee is telling us is that if you don't do symptom assessments in a blinded way, just forget it, we are not going to be persuaded, that's a very important message to convey and it should be very clear that that's what you want to say, because we sort of encourage that, but we don't always prevail.

CHAIRMAN DUTCHER: Doctor Simon.

DR. SIMON: Well, no, I don't think that, because I think there are other flaws than the one of non-blinded assessment. For example, I think the huge amount of missing data to me is probably more of concern, or as much of concern, as the non-blinded assessment.

But, I guess what I was going to say was that, you know, the other way of looking at it is that -- I mean, I think it is clear to me that these trials have not demonstrated superiority of the photodynamic therapy compared to the laser, and so in a sense I would take the way of looking at it that Doctor Schilsky originally outlined as the way one would have to look at it, do these trials demonstrate effectiveness of photodynamic therapy with this drug, but not necessarily superiority compared to the other

drug.

So, in this sense, I mean, the phrasing of the question really makes it difficult to answer the question, because it imposes this thing about adequate and well-controlled trials.

DR. TEMPLE: That's in the law, you have to be able to --

DR. SIMON: Okay.

DR. TEMPLE: -- the requirement is that you swallow hard and say yes if you want to say yes, and no if you don't.

DR. SIMON: I think the other way of looking at here is, is photodynamic therapy with this drug effective, does it produce benefit to these patients?

We have lots of opportunities for bias in these results, but the other way of looking at it is that we have objective response data which does not, in itself, mean anything about clinical benefit, but we may take as relatively reliable indicating that photodynamic therapy is at least, and probably more effective -- at least as effective as the YAG laser in a one week to one month time frame, and that, therefore, it might be reasonable, based on these results, even with the biases, to believe that the

photodynamic therapy with this drug, that that effectiveness with regard to opening up the airways would translate into whatever degree of clinical effectiveness we are seeing with the YAG laser, not necessarily a greater degree of clinical effectiveness, but some clinical effectiveness.

So, I think, although if we are going to be concerned about precedence, and do we have well-controlled trials, and does it matter whether the protocol was designed based on superiority, then I think it's an easy call, the answer would be to recommend not approving.

But, I think it's a much harder call, in terms of just evaluating whether this body of data demonstrates some clinical benefit, because I think it's possible to interpret the data in that sense.

DR. WILLIAMS: I just want to -- I had similar problems, and some of the reasons why I went to doing all kinds of different analyses of the response data was to try to get a handle on, is there any kind of objective response that I'd say is likely to be associated with clinical benefit. And, on 44 and 45, page 44 and 45 of my review, I went into looking at three millimeter changes, or five millimeter changes, and whether or not you include the

CR interpretation of the investigator or not. So, I don't know if there's a certain change that you think is likely to be associated with benefit, but if there is, I think I've sort of listed various numbers there.

And, for instance, including the investigator's judgment of CR as being a response, there were 29 Photofrin patients that had a five millimeter change, where if you exclude that judgment there are 22 patients with a five millimeter change. So, I don't know if those sort of things are of any help, but I also tried to struggle and say, is there a degree of change which I think might be associated with benefit.

In any of the analyses I did, I did find about a third at least.

Now, the question is, did you get those pages? Okay.

DR. JOHNSON: Okay.

Well, actually, in the sponsor's information provided to us there was a comment made on page 40 that almost all the patients were symptomatic at baseline, and some achieved a tumor response without improvement in symptoms. They went on to say further in the paragraph that, nevertheless, achieving an objective tumor response, even in the absence of

demonstrated symptom improvement, is important for these late-stage patients to prevent complications from obstructing lesions, such as atelectasis and post-obstructive pneumonia.

I fully expected to hear in their presentation data following up on these patients, to tell us how many, in fact, had avoided obstruction and atelectasis, as opposed to those who had not gotten an objective response, as an example. I mean, those would be fairly easy data, it seems to me, to obtain, and if those data were available that might be added impetus to consider the approval process, it seems to me.

I didn't see those data presented, however, and I would also go back to just make the comment again that I think that it is important if we can convince ourselves that patients are symptomatically benefitted by this approach. I'm not asking the company to show superiority personally, I think comparability is fine. That wasn't really the issue that I was raising. The issue was, did it, in fact, work and, more importantly, did patients benefit from that effect.

DR. TEMPLE: I guess I think when you are talking about subjective effects, equivalence, when

you are not sure what would happen in the absence of any treatment at all, is a little dubious, and one of the things in here, perhaps, the only thing that helps you believe that in the absence of a blinded situation, and, really, the absence of a no treatment control, is the fact that there is this difference, you know, how persuasive it is I'm not sure, between what you see at one week and what you see at one month.

Now, of course, by then people may well have known what had happened with the response, so maybe that influenced it, but it might be too soon for them to know that. It's one piece of evidence that, perhaps, people were actually observing what was happening, and that there was some reality to it.

I'm not trying to make more of it than it is, but, you know, we are pretty skeptical of symptomatic improvement in the absence of a control agent, you know, in the absence of showing a difference. These are not terribly well established measurements, and we'd always be suspicious.

That's the one suggestion of a difference, moderately strong, moderately persistent, across several different sets of symptoms, that's the one thing that looks sort of interesting in there to me.

DR. DeLAP: I'd just make one or two suggestions here.

If it's the belief that the data are so problematic that no rational judgments can be made, I think that's certainly one issue, and we can't help, you know, there's no resolution for that that's going to satisfy anybody.

There is, I think when you are talking about the rule of adequate and well-controlled, again, that's how we measure whether a study addresses a question or not in a fashion that we can rely on for regulatory determination. A study can certainly be adequate and well-controlled for some endpoints and not for others, or it can be adequate and well-controlled to establish, to the satisfaction of the committee, some things and not others. So, if you feel that it's not adequate and well-controlled in terms of showing superiority that doesn't mean that it couldn't be adequate and well-controlled to show activity. I've heard that in some of the comments that we've heard.

The only other comment I would add is that, if there is a finding that the response rates are something that's real and meaningful, and the question comes up about the clinical benefit

endpoints, then there can certainly be some discussion over, again, the reliability of the response rates and whether you believe that, and then you would predict that that means clinical benefit but you haven't seen it yet. And, we know what that kind of thing can mean in a regulatory sense as well.

CHAIRMAN DUTCHER: Doctor Raghavan.

DR. RAGHAVAN: Not wanting to enter further into debate with my colleague from Tennessee from the other side, I think we can -- I mean, I think we all agree, we appear to degree, that the quality of the data is flawed.

On the other hand, I think what these studies show is that investigators have demonstrated an ability to measure objectively tumor size reduction, and to try to quantify it.

And, irrespective of whether the photodynamic therapy is better than, or roughly equivalent to, or inferior to, have come up with numbers that at the least tell us it's equivalent to a standard of therapy, and it, therefore, gives an alternative physical modality.

One of the difficulties that we are stuck with is that at this point in the management cascade the alternatives are relatively limited, so this is

technically applicable to patients that may not be suitable for laser therapy. And, unless one took the view, and see no reason to do this, that the investigators were so biased as to enter false data, and I have no reason to expect that, then I think we can accept from these trials that the prospective control allows us to demonstrate measurements with a standard technology and measurements with an innovative technology, and if we use the five millimeter cutoff that Doctor Williams provided the new technology may actually even be superior. It works.

And, these studies do show that it has activity in this indication.

DR. SWAIN: I guess just to respond to what Doctor Temple said about the one month response data, looking at that, I really still have a big problem with this because of the missing data, 50 percent on one arm and about 30 some percent on the other, and I really don't see how we can make -- give an answer to that.

Plus, Derek just said he felt that they were equivalent, and, again, I think that's a big problem when you look at all the missing data.

DR. WILLIAMS: Are you talking about the

response data then?

DR. SWAIN: Right.

DR. WILLIAMS: Yes. Certainly , you say a response is at least this, saying that it might no t have been higher on the other arm you couldn't say . And, the problems that I had with the cutoff at on e month, I did an analyses that didn't cut off at on e month, so you can look at a comparative analysi s there, but you can certainly say that the response wa s at least this, as we do in uncontrolled studies.

DR. SCHILSKY: I think it's pr etty clear, though, what we are all grappling with, I guess, i s what level of confidence to have in the data. And , because in my mind this is a very elegant technique, it ought to work, I think it does work.

I'm not sure how well it works, and I' m not sure which patients are the right ones to use it with, and I think that's where we are all having a lo t of difficulty.

It makes sense that if someone has a n obstructive bronchus, and you open up tha t obstruction, that that patient ought to b e symptomatically improved. Now, you could also argue that these are patients with l ung cancer and probably have other chronic pulmonary disease, and that maybe

they won't be better, or maybe they won't be as much improved as you might have exp ected just by virtue of opening an obstructed bronchus because they have a lot of other pulmonary problems, but certainly there ough t to be some logical relationship between producin g regression of the tumor and producing symptomati c improvement.

I'm actually, in my own mind, prepared to accept the notion that that is the case. I just don' t know if that happens 50 percent of the time, 3 0 percent of the time or 15 percent of the time, and I think that's, for me, where the problem still lies.

CHAIRMAN DUTCHER: Doctor Simon.

DR. SIMON: Well, I pretty much agree wit h what you just said, Rich, except that I think - - except the last part, I think even if you look at the symptomatic improvement at one month there's n o indica tion that it's, even if you take the data a t face value, anywhere near 50 percent. You know, i f you look at Table 8 for dyspnea, for the two studies combined, improved with photodynamic therapy was 3 0 percent, and if you look at Table 10, which was chang e in cough from baseline, for the two studies combined for photodynamic therapy it was 27 percent.

Now, if there's some bias in here it' s

less than that, or if one month turns out to be the optimal time, you know, so that's probably the level of improvement, if we take the data at face value, is of the order of a quarter of the patients, probably at best, and that's then the tradeoff between that and the side effects of the therapy.

DR. TEMPLE: Do you all think that's a low rate of clinical benefit in an oncologic trial or a high rate of benefit in an oncologic trial? No, I'm serious, these are people with a progressive disease. If you believe those numbers, and I think they must be exaggerated probably, because it was unblinded, that's more than we usually see outside of leukemias and stuff like that.

DR. SIMON: Well, you did have a 19 percent incidence of life-threatening adverse events, so if you take that at face value too, then that's where you are going.

DR. TEMPLE: Well, if that's important, one has to pin down how many of those were life threatening and how many were severe.

DR. SIMON: It didn't say severe, it said life threatening, that was just the pure life threatening. That was, I think, in Table 22.

DR. JOHNSON: The answer, while we are

looking that up, I think the answer is always that it depends.

DR. SIMON: Very severe life threatening.

DR. JOHNSON: You know, 25 percent response rates is not real good in germ cell neoplasms, but it's pretty darn good in lung cancer, but that was a symptomatic response, not an objective response that we were talking about, and that's subject to bias, I think, the way those data were acquired.

DR. TEMPLE: Oh, I don't disagree with that at all. If you believed it, though, it wouldn't be too shabby.

DR. JOHNSON: No, no, it would be okay, but the life threatening events, and, again, we looked at that, or attempted to bring that out, I agree with you, grade IV alopecia is not life threatening, it might affect your life in some way, you know, quality of life, but not your quantity of life, perhaps.

But, fatal massive hemoptysis in a respiratory event does, and when I add those things up together, in the randomized data, I think that's a statistically, as well as a clinically, meaningful difference in a treatment that doesn't alter the life of the patient, and you haven't persuaded me that it

improves the quality of the life of the patient.

Those are the facts as I see them. We are sort of straying off the question that was asked, but I mean that's sort of how I sum up these data for this first group of patients.

DR. TEMPLE: As these were going by, I could not tell, maybe I just wasn't looking close enough, how many of those events were, in fact, life threatening and how many were severe forms of non-life threatening. That's obviously crucial, maybe that needs to be pinned down. It's a defective category. You are not supposed to add severe and life threatening, you are supposed to add serious and life threatening.

DR. SIMON: This says very severe or life threatening.

DR. TEMPLE: Yes, but, see, very severe means it's a severe version of whatever it is, it doesn't mean that it had any life-threatening capability.

DR. SIMON: Well, the only thing is, the 25 percent we were just talking about, these are not life saving either, so --

DR. TEMPLE: No, that's fear, but, I mean, one needs to know what those are, if they really are

life threatening that would be very bad.

DR. SIMON: I do think that some of th e event s that were reported as adverse events i n patients with progressing lung cancer, we don't reall y know what's Photofrin related and what's -- you know, you can look at the comparison s between the two arms, but certainly I think it would n't be fair to say they are all from Photofrin. If you can see a difference in the two arms --

DR. JOHNSON: No, I'm not sugg esting that they are, but the two arms allegedly are the same kin d of patient.

DR. WILLIAMS: Right.

DR. JOHNSON: So, the fact that there's a n excess number on one arm versus the other arm.

DR. WILLIAMS: Okay, you are talking abou t the 19 versus eight.

DR. JOHNSON: Among other numbers, yes.

DR. WILLIAMS: Right.

DR. TEMPLE: Grant, this shouldn't be don e without knowledge. Only ten percent of them wer e within 30 days of the procedur es, that might help you make a statement about plausib ility, but someone must know what they are. Why are we asking?

DR. JOHNSON: Let's -- you know, again, w e

are straying off, but since you brought it up, I mean, who made 30 days the magic day that this is not a problem related to the product and to the treatment?

In fact, I mean I don't personally believe it is, but the fact of the matter is, the response to PDT was slower than the response to YAG. Who is to say that the complications to PDT might not be more prolonged or later developing than the complications to YAG? I don't think that 30 days is a magical day in my mind, and if someone has had EBT therapy, and then gets some other form of therapy that may further affect the integrity of the bronchial mucosa, I could see where one could very plausibly get an increased instance of fatal massive hemoptysis.

Now, I didn't want to say that earlier, but that, in fact, is I think something that needs to be considered. If we are going to look at the data, flawed as they are, then we need to begin scrutinizing the data with all of the possible explanations.

DR. SCHILSKY: The striking thing in this whole conversation to me is, we keep going around and around I think on the same points, or we keep coming back to the phrase, we don't know. So, after all this discussion this afternoon it seems that we don't know how good this treatment is and we don't know how toxic

it might be. And, if we don't know those two things, I don't see how we can recommend that this treatment be sold in American medicine.

DR. TEMPLE: In this case, we do know. On page 48 it says there were seven patients with hemoptysis in one group and four in the other. Whether 30 days is a magic time or not could be debated, obviously, but within 30 days two in the PDT group and three in the YAG group, so that's the hemoptysis thing.

But, someone knows what these other adverse reactions are. They've been reported, but no one seems willing to say. The company knows what they are, they have a slide on it. Why won't they show it?

DR. JOHNSON: Again, they did have a slide, Bob, and they showed those data, and they showed it on slide 33, where in their alleged key studies there were ten events that were called massive fatal hemoptysis, or fatal massive hemoptysis in the P-17 and P-503. That was a ten percent instance.

And, in the YAG group there were six such incidences. Okay. I agree that that's not statistically or maybe even clinically relevant, that's not my point, I'm not trying to argue that. The very next page, on slide 35, they talk about life

threatening, they didn't call them serious, they called them life threatening, to me that means it threatens your life, respiratory insufficiency five and one.

DR. WILLIAMS: They have a slide up there that works good.

DR. JOHNSON: Now, if I add those up, I'm not really interested in looking at that slide at the moment, if I add those up, and I realize coming from Tennessee there's some danger in my doing this, but five and ten equals 15, the last time I checked, and six and one equals seven, and I think if you do a qui square analysis on that, that's going to be statistically significant.

UNIDENTIFIED SPEAKER: .09.

DR. JOHNSON: Yes, with all these data, but I'm asking about, again, you know, I'm asking about the two major events, respiratory insufficiency and hemoptysis.

DR. AZAB: All the respiratory insufficiency recovered except one. The only respiratory insufficiency, as I mentioned, it --

DR. JOHNSON: It's not a question of whether they recover or not.

DR. AZAB: -- you are right, I'm just

explaining.

DR. JOHNSON: It's life threatening, and that means they may not recover.

DR. AZAB: Yes, it is true, but if you look at the whole group of life-threatening pulmonary events this was not one of two events, these were several ones, one was a repeat of severe dyspnea, one where abnormal chest X-rays, pleural effusions, pneumonia, there was a respiratory insufficiency also in the nd:YAG arm, this is looking at all adverse events at any time during the follow-up of the study, not cutting within 30 days or without 30 days. So, that's the total group, 17 per cent and seven percent.

And also, if you look at it in terms of the overall death within 30 days or beyond 30 days in the trial, and if you look at the survival curves, the incidents were similar.

It's just that the details of the pulmonary events you have discussed.

CHAIRMAN DUTCHER: Let me summarize. From the discussion and from the data that was presented, it seems that we know -- yes - - it seems that we know that some tumors shrink. Patients whose tumors shrink, some of them feel better and some of them don't, and we can't really determine who is who, and

we can also see that some people get sicker and some people have adverse events, and it seems like there's an increased number of those people who get this particular therapy.

And, it seems to me the sense of the committee is that this therapy is also available for given individuals, whether it's approved by this group or recommended by this group or not.

So, I think we've said everything we can say. There's a lot of concerns raised, so I think we have to do some voting. Do you want an answer to that question?

DR. TEMPLE: Yes, sure. I was trying to actually think of whether we should say anything about the, it's available anyway point.

CHAIRMAN DUTCHER: You are welcome to. I know we are not supposed to say that.

DR. TEMPLE: Well, we are criticized severely, I should tell you, for not having uses that all oncologists recognize as effective, in quotes, you know, in the labeling, and we are at least sensitive to that, that to the extent labeling is irrelevant to what people actually do, people tend to disregard it and say bad things about having standards, and that worries us.

One of the remedies that's bee n proposed, although not this year in Congress, is to put new use s in the labeling if a lot of ex perts think they belong there. That would not be my favorite choice for the new effectiveness standard.

So, I'm a little -- this is on my mind as we think of it, so I guess I would hope that you don' t take too much reassurance from the fact that it's out there, in trying to think of whether it makes it o r not, you should try to have a standard that looks at the data and don't think about that too much, much in the way you shouldn't think about how much thing s cost, even though one can hardly avoid it.

So, what we'd like to hear is whether you think collectively, with all its flaws, these dat a make it or not, and don't be particularly reassured b y the fact that people can use it anyway, if you ca n help it.

CHAIRMAN DUTCHER: So, for all those who believe that these two trials served as adequate and well-controlled trials demonstrating the efficacy of Photofrin for the treatment of patients with partiall y or completely obstructing endobronchial non-small cel l lung cancer, please, raise your hand.

There is no hand raised, so it's a

unanimous no.

All right, we need to take a no vote. All those who feel that they do not, please, raise your hand. Eight, nine, is it nine?

All those who abstain? I can't see hands at the end of the table. One, two.

We are missing -- Doctor Krook, what was your vote?

DR. KROOK: No.

CHAIRMAN DUTCHER: No, so there were ten no and two abstentions. Okay.

The second question is with regard to toxicity. I can read the question, considering the balance of efficacy and toxicity demonstrated in these trials, should Photofrin be approved for reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobronchial non-small cell lung cancer.

All those who would vote to approve this raise your hand.

DR. TEMPLE: Well, you don't really have to answer that, you already told us there was no evidence of effectiveness.

DR. JOHNSON: No, we just said the trials were no good, it didn't mean we didn't want to prove

it.

DR. TEMPLE: What?

DR. JOHNSON: That just says you are not having this in the discussion.

DR. TEMPLE: Well, if you tell us there are no adequate and well-controlled studies, I can assure you we turn it down. There's no legal way to approve it.

Okay, maybe you don't know that, so let me make it clear. It would be a violation of the law for us to approve a drug if there are no adequate and well-controlled studies to support approval.

DR. JOHNSON: Who goes to jail, us or you?

DR. TEMPLE: We do, but the main thrust is, we can't follow your advice, if you tell us there are no well-controlled studies but we should approve it, we will say, thank you, but we can't. We have no choice in that.

DR. JOHNSON: That's fine.

CHAIRMAN DUTCHER: Okay.

So, considering -- so, we don't need to answer this question.

So now, superficial lung cancer indications.

DR. TEMPLE: Was I remiss in not making

that clear earlier? I feel bad about this.

CHAIRMAN DUTCHER: Well, I think there are some new people that, perhaps, haven't heard you say that, but --

DR. TEMPLE: Okay, just to pin it down, the requirements of law for approval that relate to effectiveness are that there must be substantial evidence of effectiveness, and the law is unequivocal in saying the only basis for finding substantial evidence of effectiveness is adequate and well-controlled studies that are persuasive to experts. That doesn't mean the studies have to be perfect, they have to be -- that's what I meant before by saying, you have to swallow hard sometimes, it includes historical controls, which in another world people would describe as uncontrolled studies, but they can be well-controlled studies according to our regulations. But, one has to be able to say that these are well-controlled studies, otherwise they can't serve as a basis for approval.

They could be well-controlled studies of a surrogate endpoint. They could be studies of response rate, if people found that persuasive, but they have to be well-controlled studies.

DR. SIMON: Is the distinction between

these two questions that you might find adequate and well-controlled studies demonstrating effectiveness of the agent, but you might still not recommend it because the degree of effectiveness is not commensurate with the degree of toxicity?

DR. TEMPLE: Absolutely. The second part of approving a drug is that you have to conclude that it's safe for its effective use, and safe is inherently a comparative statement, that means the benefits have to outweigh the risks. So, that's why we ask it in that order, you sort of, you have to decide that it does something first, and then you weigh the evidence of toxicity against the evidence of benefit and make a second judgment.

DR. MARGOLIN: I think part of the confusion may have been, even for those of us who have been around for a while, that usually these kinds of questions are worded that, that would be part 1A, and then part 1B would say, if so, should we approve it.

DR. TEMPLE: We'll watch that next time.

DR. RAGHAVAN: I'd hate to think of Doctor Temple, even though he's publicly -- I thought I heard him publicly admit he was out of his mind about 15 seconds ago, but I would hate him to lose sleep over this. I mean, I don't have to -- I understand the law

as it stands, and my vote was an abstention because I choked on the thought that these were adequate and well-controlled.

On the other hand, as I explained, there was the universe of knowledge which influenced my vote. In the context of the voting pattern of the committee, my vote became irrelevant.

CHAIRMAN DUTCHER: Superficial lung cancer indication, the applicant has collected a group of patients with early lung cancer in whom surgery and radiation are said to be contraindicated. Do the 24 indication patients represent a group of patients with no standard therapeutic option? If not, can you recommend criteria for selecting such a group?

Comments?

DR. JOHNSON: I'll make a quick comment about this. I actually think that to the extent that it's possible to do, they've selected a group of patients in whom, certainly, surgery and/or radiation therapy, in a curative sense, would be extraordinarily difficult, and I don't think one could ever, in a clear cut, black and white manner say that this patient is or is not a candidate for curative therapy.

But, I think to the extent that that's possible, they've done that with these criteria. So,

my personal view is that they have demonstrated a group of patients, those with extraordinarily poor pulmonary function, those who may have received prior curative or radiation, and, therefore, no longer are able to receive additional radiation therapy, and certainly an assessment by a skilled thoracic surgeon to suggest that this patient is inoperable is very persuasive that that patient is inoperable.

So, I would think yes.

CHAIRMAN DUTCHER: Doctor Raghavan.

DR. RAGHAVAN: I really thought this would be a relatively quick one. I agree with everything Doctor Johnson said, except his last comment. And, my reason for that is the one thing that they haven't convinced me of is that all of these patients actually have cancer. In the absence of histological review and a notoriously difficult histological entity, I don't see how we can draw those conclusions.

DR. TEMPLE: Is that everybody or just the in situ?

DR. RAGHAVAN: The in situ.

DR. TEMPLE: And, not all of these patients are in situ.

DR. RAGHAVAN: I mean, I think the clinical trial's histological review is important. I

think that for clinical trials of this importance, histological -- central histopathological review is of critical importance. I think it's harder to make a mistake about cancer versus no cancer in T1/T2 disease, although it's been done. Every cancer center will see patients, allegedly, with cancer, who upon histological review don't have it.

But, in TIS, it's a frequent error.

DR. SCHILSKY: Just one additional comment. I mean, I think to be, I guess, precise, the criteria that were put forward to select patients to be in the indication group didn't include anything about the diagnosis. And so, personally, I agree that these are reasonable criteria for selecting patients who are not operable.

The criteria for the study, for enrolling the patient in the study, obviously, relate to the diagnosis. So, I think, in my mind, it's perfectly reasonable to say that these patients should not be considered candidates for surgery or a curative radiation. I don't think the histology factors into this particular question, although it clearly factors into the discussion about whether those patients should be included in this data set, or, you know, in the global analysis of these data.

CHAIRMAN DUTCHER: All those who think that the 24 indication patients represent a group of patients with no standard therapeutic option, please, raise your hand, high. Ten.

Voting no? One.

Are we missing somebody? Did someone not vote?

Abstention?

Is that right? Okay.

The following -- read the table -- this is in the new handout that was in the folder for those of you that are reading the wrong set of questions, the following are histologically documented complete response rates, where it describes -- does everyone have this -- where it describes median survival, 3.5 years, 3.4 years for the indication group.

DR. WILLIAMS: It's a separate sheet.

CHAIRMAN DUTCHER: It's a separate sheet.

DR. MARGOLIN: It's the one with A and B at the bottom, right?

CHAIRMAN DUTCHER: Right, with A and B at the bottom. And then, at the very last, in the group of patients with T1 disease the histological complete response rates were three months CR1, 51 percent, one year CR1, 31 percent. (A) Should Photofrin be

approved for treatment of endobronchial carcinoma in situ or microinvasive non-small cell lung cancer in patients for whom surgery and radiotherapy are not indicated?

I think we've talked a lot about the micro -- the in situ, and the issues of its histology, so should we just vote on this? Does anyone want to clarify their position?

DR. JOHNSON: Well --

CHAIRMAN DUTCHER: B excludes the -- no, B does not exclude -- B excludes the in situ.

DR. TEMPLE: You could vote on them separately, if you want.

CHAIRMAN DUTCHER: Do you want to vote on B first?

DR. TEMPLE: Well, I mean, you could vote on tumor in situ as one possible claim, and microinvasive as another, if you think that's a better division, which obviously some people do.

DR. JOHNSON: I guess I'm not familiar with the term microinvasive in the context of this, because, presumably, you are meaning a T1 lesion here, is that correct?

DR. WILLIAMS: Correct. The original wording was microinvasive, and I guess the patient s

were radiologically occult, and most of them T1, I certainly don't want it approved for T2.

So, I think here we are talking about microinvasive, that is small T1s, microinvasive T1s.

DR. JOHNSON: Because, certainly, the word microinvasive has a different connotation in some tumor types and how one approaches them. I wonder if we might -- well, I suppose, let's deal with A first, and then I guess we could deal with -- it seems like A precludes B, I don't know, because it says, or microinvasive. It says, endobronchial carcinoma in situ or microinvasive.

DR. WILLIAMS: Well, the original indication was, basically, it means approving for both. I think it would be better for you to do it CIS and then T1, or microinvasive.

DR. TEMPLE: Do it separately, we can put it together.

DR. JOHNSON: Okay.

CHAIRMAN DUTCHER: Okay.

Should Photofrin be approved for treatment of endobronchial carcinoma in situ, in non-small cell lung cancer patients for whom surgery and radiotherapy are not indicated?

Doctor Simon.

DR. SIMON: I guess I just want to have a little clarification, maybe a little discussion here. I mean, one problem I have with this is, it seems to me it's probably -- is it actually possible to do randomized clinical trials in this sort of setting? It seems like it's such a rare -- unless I'm wrong, please correct me, are the number of patients such that you could ever really do randomized clinical trials for this kind of a subset of patients? So, I guess I'd like to hear some discussion of that here, and I guess the other thing I'm somewhat -- I mean, it seems to me there's two points of view you could have to the superficial set of patients. One is, well, how do we really know, how do we really know that these patients benefitted, that they wouldn't recurred just as early because of other sites of disease, they wouldn't have died just at the same time, we really didn't have a control group, we really didn't have -- we don't have good historical control data, so there's that point of view.

And, the other point of view is, certainly, when we are talking about invasive cancer, is that these patients have tumors that those may not be the lesion, the lesions being treated may not be the ones that are going to kill them, but they are

probably -- history is probably pretty good in saying that those lesions are not going to go away by themselves, and that there's no other treatment available for those patients, or for those lesions.

And, on that basis -- and it's probably not possible to do randomized clinical trials for that set of patients -- so, I don't know, that combination of things would tend to make me favor approval. So, I'd like to hear some discussion of that.

CHAIRMAN DUTCHER: Doctor Krook?

DR. KROOK: I agree with you, I don't believe you can do a randomized trial in this group. I think they are rare. I don't think that, at least in my experience, you can get people to accept an observation versus doing X, or Photofrin, or otherwise, and I agree with you, as a clinician.

CHAIRMAN DUTCHER: Doctor Raghavan.

DR. RAGHAVAN: Yes. I think you have a misapprehension here, because I think you can do well-structured trials. I think the problem that exists with the database we have here is, and it could actually be that that database could be fixed by getting histological review, we don't know what's been treated, and that's the problem here. It may well be that the company can go back to its centers, get the

slides out and do a resubmission, demonstrating exactly with histologically controlled accuracy, what they've treated. That's the problem here.

I don't think that you'd need to do a randomized clinical trial anymore than these days would be appropriate to do an observation versus therapy trial for carcinoma in situ of the cervix. That was done in New Zealand and the subject of major litigation less than 15 years ago, but I think the issue is that one could, in fact, salvage the database here in a relatively simple fashion.

Now, whether that requires the company and the FDA to get together and do it in an office session, as opposed to at this committee, I'm not sure, but I think these data could be salvaged by histological review. I don't think you'd have to start from square one.

If the data showed that upon review non-cancers were treated, the company has a mega problem. If the data show that real cancer in situ was treated and T1 disease, then I think the whole context of this second half of the discussion would change.

DR. TEMPLE: It seems important to tease two separate questions out. One is whether the studies actually showed anything, which is what you

are really asking, because you don't know whether the people have the disease.

If the committee in general thinks that we should make sure the histopath is reviewed, we can certainly do that.

But, apart from that, I thought I heard questions before about whether it's worth treating tumor in situ at all, and several people said, yes, absolutely, they could do a randomized trial. So, I'm a little confused by some of the discussion that's followed here, or maybe it's just a debatable question, that's why.

DR. MARGOLIN: I'm not at all an expert in lung cancer, but, certainly, it sounds like Doctor Johnson was willing to say that we really don't know as much as we need to about the natural history of these early pre-invasive or microinvasive cancers, and, furthermore, in terms of the patients that were selected in this indication group, the way they were picked was not based on symptoms that led to the finding of a radiographically transparent endobronchial lesion, but they were -- at least we were told that these were screening and follow-up bronchoscopies and cytologies, things that I don't think are standard or routine for the lung cancer

community, which means I'm not sure how representative they are of community practice.

Furthermore, I think knowing would be essential, and was suggested here with the pathology review and the case review, that we know where the relapses occurred and, truly, what, if we can't tell what the natural history of the disease would be in this trial, which wasn't controlled, at least to know the natural history of the relapses in this treated group of a subset of a subset of patients who even came to the trial by a very strange route.

DR. SWAIN: I'd just like to comment too, and I also heard Doctor Johnson say that he thought the trial could be done, the reason why I was the only one to vote for no for the first one was because I was not clear at all that we know what to do for these patients. Everybody has kind of said that, so I don't think those ten patients that were included with TIS, if they have it, were really clearly a clear indication for this therapy at all. I don't think we have that answer.

And, if Doctor Johnson is right, and it's a field effect, not just a local effect, then we certainly should be doing randomized trials with other agents.

DR. TEMPLE: That relates to tumor in situ. So, you think there's doubt about whether we know that that should be treated, therefore, it's hard to give an indication for it.

DR. JOHNSON: Well, I think we all know that it ought to be treated. The question is, with what? I mean, because carcinoma in situ eventually evolves into carcinoma, in most instances, and it's been certainly the paradigm for other tumor types, where that type of pre-malignant process exists.

But, that's why ongoing randomized -- if we can't do -- I can't believe that we would argue that this is not doable, when we've just completed a 1,400 patient trial in patients who had resectable T1 lesions, and that's why I made my caveat earlier, in whom recurrence rates has been correctly pointed out, or second primary tumor rates are high, and clearly the reason they are high is because these people have a high risk for recurrent disease. They have a field effect, and some of those are carcinomas in situ.

Now, there may be other reasons too, but we just completed a study of nothing, placebo versus vitamin A, and that's been done in head and neck cancer and other cancers, so it's not a question of it not being doable, it's doable, you just have to select

the right patients.

What I said was, you are never going to be able to do the randomized trial in this group of patients because they are very, very, very rare, and that -- you know, but I think the issue we continue to sort of confuse, I think, what this first question asked was, have they selected a group of patients, put aside for the moment the issue of were they correctly diagnosed, but were they physiologically and for other medical reasons not candidates for other forms of therapy.

I think the company attempted to select that group of patients for obvious reasons. There were not other options for these patients, and they were suggesting that maybe this approach would be beneficial.

I think it's harder to make the conclusion that it is for the TIS patients, for the reasons I have stated, we don't even know what to do with standard therapy for that group. You usually tell people to quit smoking, that's the first thing you do, and tell them to go out and eat an apple or something.

But, for the T1s, that's a different issue, but for operable patients, I think you could conceivably consider doing that, but it would be very

tough. You'd have to have a group like the Mayo group, or someone -- or the M.D. Anderson group, who has a large screening process underway, and you'd have to recruit other institutions that have a high thoracic oncology program to do it. I think it's doable.

DR. TEMPLE: But, we need to understand in the committee. Let's assume for the moment that we can show that they had tumor in situ, and let's assume for the moment, as you just answered, that a group was defined that couldn't get the alternative therapies of radiation and surgery, and that there are people, albeit not very many, who have tumor in situ, and the question is, is that -- and, I assume that people believe it was shown that you could make those lesions go away for a reasonable period of time, and that there was a complete response rate that was respectable and of adequate duration.

If you think all that, does that merit a claim? That's what this question is. Or, is there so much uncertainty about what to do with those people that it's like recommending treatment of a non-disease.

DR. JOHNSON: I personally don't think it is. As I've said, the difference between a product

like, let's use retinoic acid, which is a systemic product that presumably affects the entire field, is a different phenomena than doing something localized in a situation where the entire aero-digestive tract is at risk for recurrent disease.

I mean, we are sort of drifting off this issue a little bit, but I think it's a tough one when you are talking about these carcinomas in situ.

And, this is my practice, that along with breast, and, I mean, I see hundreds of patients every year, these are not common patients, you know, they are not common, unless you have a program that is specifically addressing this issue. So, it's hard to answer the question, I think, Bob, is the real issue that we are wrestling with.

CHAIRMAN DUTCHER: Doctor Simon.

DR. SIMON: I just want to get clear on this point, so the -- what would the randomized trial be, you'd do it in operable patients?

DR. JOHNSON: Well, yes, I was going to say, there are several ways that we could debate the design of the study, but, again, this is taking a subset of a subset of a patient population, so to ask if you could do a randomized trial in such a group of patients would be like asking, could you do a study in

a thousand left handed Tennesseans that, you know, live at my house. You know, they are not many of them.

DR. TEMPLE: Well, there'd be no reason to do the trial only in people who were non-surgical and non -- I mean, if you want to find out what the value of treating tumor in situ is, you can study that in a broader population, you still have to study it is.

DR. JOHNSON: Yes, I agree with that.

DR. SIMON: I guess I am lost by the logic somewhat. It seems like the claim is for the treatment of patients who are not surgical candidates and not radiotherapy candidates. They are not claiming that this treatment is as good as surgical resection, and so whether you could do such a trial, which I think is -- you know, I don't know whether you could do such a trial comparing it to --

DR. JOHNSON: I think the issue is --

DR. SIMON: -- you know, I mean, I think is sort of not directly relevant.

DR. JOHNSON: -- well, it is relevant, because it suggests that by selecting this group of patients that one might have operated upon a patient had they been, and they would have, therefore, benefitted by that.

And, even that is debatable, i s my point.

DR. TEMPLE: I understood the trial to be one of treatment with something versus watchfu l waitin g. In fact, I thought that's what we talke d about before.

DR. JOHNSON: No, I am, but I' m answering Rich's question.

DR. TEMPLE: Well, that's the answer , that's what you'd need to demonstrate, otherwis e there' s no point in recommending treatment if yo u don't know if treatment of any kind does any good.

DR. JOHNSON: It's a controversial are a that actually, at the risk of seemingly abandoning my alleged unbiased position here, as Doctor Pass and I happen to co-edit a book on lung cancer, and one o f the things that we wrestled with is how do you presen t data about management of this very group of patients. It's a very difficult group of patients.

And, we actually have debated as recently as six days ago at an editorial board meeting abou t whet her to include this group of patients as a separate entity to discuss wit hin the context of this text book.

So, I mean, these are issues that ar e problematic. So, I think when you ask us, can we mak e

a conclusion on the basis of about ten patients whether this approach has made any relevant benefit to this group of patients, I just don't see how one can conclude the answer to that is anything but no.

Now, that's why I'm glad you separated these questions, because I think there's another issue here that I feel a little bit more comfortable about saying another answer.

CHAIRMAN DUTCHER: All right.

So, let's vote on A. And, A is only endobronchial carcinoma in situ. All those -- what?

DR. RAGHAVAN: Could you just clarify, is this subject to histological review, in other words, to what --

CHAIRMAN DUTCHER: Yes, subject to histologic review confirming that the patients that we were presented all had the diagnosis of carcinoma in situ.

DR. RAGHAVAN: And, they are not surgical candidates.

CHAIRMAN DUTCHER: This is for the subset of not -- surgery or radiotherapy are not indicated.

DR. TEMPLE: That would be the claim, we wouldn't spend more time confirming that they weren't, right.

DR. JOHNSON: And, let's be sure, how many of those 24 patients had TIS? Ten, right?

DR. MARGOLIN: Well, it was 42 percent.

DR. WILLIAMS: They do have ten, the philosophy we took in this was to look at the overall rate of response in the overall group, and to make sure that there were such patients within the indication group.

DR. TEMPLE: But, am I right in that, were there ten that --

CHAIRMAN DUTCHER: Forty-two percent.

DR. JOHNSON: Forty-two percent what?

DR. TEMPLE: But, Grant is making the point that if you are interested in whether this lesion responds, you can look at the whole group, not just the indication group, because whether someone can get a knife where the lesion is probably doesn't have anything to do whether it responds. I mean, that's the theory anyway.

So, it's a larger experience with tumor in situ than just the indication group.

DR. JOHNSON: I know, and maybe this --

CHAIRMAN DUTCHER: It's 20 out of 100.

DR. JOHNSON: -- right, maybe this is being too picky on this, but we were asked again for

a group in whom surgery and radiation therapy were not indicated, and we had a panel of experts go through this group and they by consensus came to the conclusion that those 24 were clearly not treatable in that manner.

I understand the biological difference, I'm just trying -- because the indication, though, is for those who are not candidates for surgery or radiotherapy.

DR. TEMPLE: The indication is for those, but the evidence of effectiveness, according to the way --

DR. JOHNSON: Yes, I understand.

DR. TEMPLE: -- it was completed could come from a larger group.

DR. JOHNSON: Okay.

CHAIRMAN DUTCHER: Does everybody understand where we are at this point?

Okay. Should Photofrin be approved for treatment of endobronchial carcinoma in situ, given all the discussion about what it is, and how it isn't treated, in patients for whom surgery and radiotherapy are not indicated? All those who say it should be approved raise your hand. Four.

All those who feel it should not be

approved for in situ? Seven.

Okay.

Should Photofrin be approved for treatment of T1 non-small cell lung cancer in patients for whom surgery and radiotherapy are not indicated?

Discussion, brief discussion, no discussion.

Doctor Schilsky.

DR. SCHILSKY: No one else is going to discuss anything.

I just -- I guess I just wanted to, I don't know, offer a cautionary note, which doesn't necessarily bear on the way I'm going to vote. My personal opinion is that the answer to this question should be yes, because I do think that in this group of patients, for whom there are no other options, who clearly have an invasive cancer and for whom the outcomes look pretty good, albeit small numbers and not well-controlled studies, I 'm prepared to say yes.

My cautionary note, I guess, is that -- which is not directly relevant to this, but I have a concern about whether or not this therapy might be applied in patients with T1 tumors who are candidates for resection, and, you know, of course, I guess the argument could be made, well, you could do that right

now because the drug is out there, but, you know, I don't know if anyone else on the panel would share my concerns, but it seems to me that it's a sort of an easy thing to imagine why somebody might not be a good candidate for surgery or radio therapy, you know, that it's not clearly within these fairly rigorous criteria that have been established by the experts, and then to just say, well, we've go this Photofrin stuff we'll give them, treat them with that.

So, I think that the data that we have would support recommending Photofrin for this group of patients, although I do have some concerns about how it will ultimately be used in the medical community, not entirely germane, but I wanted to express that.

DR. JOHNSON: Yes, well, I think it's a very relevant point, and I think it should be pointed out that T1 resectable lesions, that are truly T1 and are node negative, those patients have a pretty good five year survival rate that's somewhat dependent on histology as high as 85 percent in those with squamous cell carcinomas, maybe 70 percent in those with adenocarcinoma, so it's a group of patients, those are pathologically staged patients, but still, that's a group of patients that does quite well with standard resection.

And, unfortunately, again, in my practice I can say categorically that we see patients that have been deemed "unresectable," but have never seen a thoracic surgeon, for example. And, when they, in fact, go to a thoracic surgeon, someone who is accustomed to doing that type of work, they clearly become resectable.

DR. SCHILSKY: This may cut down on referrals to thoracic surgeons, because pulmonologists may just pull out the Photofrin.

DR. SIMON: Can -- I guess there's nothing you can do about that in the labeling?

DR. TEMPLE: Put really unresectable.

DR. SIMON: Really, really.

DR. JOHNSON: Perhaps, you could store it in thoracic surgeons' offices.

DR. TEMPLE: We can think about how to emphasize that.

CHAIRMAN DUTCHER: Yes.

MR. GIDDES: As a lung cancer survivor, I would think that I would like to -- I'd go yes on this, because your treatment is right away. The only other thing I can think of, you'd have chemo, and I can tell you, going through chemo, you have a long waiting game that is very taxing to your family and

yourself, where I assume this you could hear, you know, within 30 days or so.

DR. MARGOLIN: I'm sorry, but clarify that, that's not quite right. The distinction in treatments in these patients is not going to be chemo versus Photofrin.

MR. GIDDES: No, but if you don't do surgery or radiation, what other ways are you going to handle T1?

DR. JOHNSON: Well, again, it's a matter -- it's what deemed resectable and unresectable, it's all in the mind of the surgeon to a certain degree, and there are techniques available today that would permit one to do surgical resection in patients in whom one might not do a standard type of procedure, for example. And, we don't know that that necessarily would be beneficial, but, again, I happen to agree that this is an indication that makes more sense to me than some of the others that we've talked about today.

DR. MARGOLIN: I think we're talking about curative modalities here, and so even if patients are not -- have major contraindications to surgery or external beam radiation, some of the brachytherapies, as well as we haven't talked about the YAG laser for these lesions, but I imagine in some patients that

would also be an option. But, chemotherapy doesn't have curative potential for this.

CHAIRMAN DUTCHER: Can we vote? Okay.

Should Photofrin be approved for treatment of T1 non-small cell lung cancer in patients for whom surgery and radiotherapy are not indicated after pathology review?

DR. WILLIAMS: Could I make a comment? The QLT had suggested microinvasive, I think for a good reason, T1 goes up to three centimeters.

CHAIRMAN DUTCHER: Okay.

DR. WILLIAMS: So, I don't really think -- I think their original suggestion is more realistic, unless you want the people to treat three centimeter tumors with --

DR. JOHNSON: Well then, they are going to have to define microinvasive. I mean, I think that that's not a term that one normally uses in this --

DR. WILLIAMS: Right, right.

DR. JOHNSON: -- situation.

DR. WILLIAMS: Well, we can work on that. We could use T1 and qualify it --

DR. JOHNSON: Yes.

DR. WILLIAMS: -- with the size and depth of invasion or something.

CHAIRMAN DUTCHER: And, you can define the loss of -- the degree of poor protoplasm that would be the indicated patient. All right.

DR. WILLIAMS: That's the other thing that we can discuss, is how to define that group.

CHAIRMAN DUTCHER: Right.

DR. WILLIAMS: If we should, and how to define the group further.

CHAIRMAN DUTCHER: All those who would vote to approve? Nine.

Those who would vote no?

DR. OZOLS: Abstain.

CHAIRMAN DUTCHER: Abstained, Doctor Ozols.

Well, any other comments from the committee?

Okay, thank you very much, the meeting is adjourned. We will start tomorrow morning at 8:30.

(Whereupon, the meeting was recessed at 5:10 p.m., to reconvene at 8:30 a.m., tomorrow morning.)